JC05 Rec'd PCT/PTO 20 JUL 2001

FORM PTO-1390 U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE
REV. 2/01

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
07579.0014

U.S. APPLICATION NO (If known, see 37CFR1.5)
09/889701

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/AU00/00103	February 15, 2000	February 15, 1999

TITLE OF INVENTION
PRODUCTION OF ISOFLAVONE DERIVATIVES

APPLICANT(S) FOR DO/EO/US
Andrew HEATON and Naresh KUMAR

Applicant(s) herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2)).
   - a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   - b. ☐ has been communicated by the International Bureau.
   - c. ☐ is not required, as the application was filed with the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
   - a. ☐ is attached hereto.
   - b. ☐ has been previously submitted under 35 U.S.C. 154 (d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)).
   - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   - b. ☐ have been communicated by the International Bureau.
   - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☒ Annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A Substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154 (d)(4).
19. ☐ A second copy of the English language translation of the international application 35 U.S.C. 154 (d)(4).
20. ☒ Other items or information:
   - a. ☒ Copy of cover page of International Publication No. WO 00/49009
   - b. ☐ Copy of Notification of Missing Requirements.
   - c. ☐

JC18 Rec'd PCT/PTO 2 0 JUL 2001

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 09/889701	INTERNATIONAL APPLICATION NO. PCT/AU00/00103	ATTORNEY'S DOCKET NUMBER 07579.0014

21. ☒ The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33 (1)-(4) **$100.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =				$1,000.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				$	
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total Claims	116	- 20 =	96	x $18.00	$1,728.00
Independent Claims	8	-3 =	5	x $80.00	$ 400.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+$270.00	$ 270.00
TOTAL OF THE ABOVE CALCULATIONS =					$3,398.00
☒ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.					$1,699.00
SUBTOTAL =					$1,699.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest priority date (37 CFR 1.492(f)).					$
TOTAL NATIONAL FEE =					1,699.00
Fee for recording the enclosed assignment (37 CFR 1.21 (h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property. +					$
TOTAL FEES ENCLOSED =					$1,699.00
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 1,699.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. ________ in the amount of $ ________ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING**: Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Ernest F. Chapman Reg. No. 25,961
NAME/REGISTRATION NO.

DATED: July 20, 2001

PRODUCTION OF ISOFLAVONE DERIVATIVES

Introduction

The present invention relates to the hydrogenation of isoflavones and products thereof. The invention also relates to the synthesis of phytoestrogenic isoflavone metabolites and derivatives from the hydrogenation products of isoflavones.

Background of the Invention

Isoflavone metabolites possess a very wide range of important biological properties including oestrogenic effects (WO 98/08503). Isoflavone metabolites can be isolated from the urine of human volunteers subjected to diets rich in plant isoflavanoids such as soya, lentils, peas and beans.

In spite of the recently discovered biological significance of isoflavone metabolites there is not at present a general method suitable for the large scale synthesis of these metabolites. The few reported syntheses of these metabolites utilise either catalytic hydrogenation or hydrogen transfer reduction of the corresponding isoflavones. These reduction reactions are found to be non-selective, extremely difficult to control and lead to mixtures of different products.

The reduction of 5,7-dihydroxyisoflavylium salts have been reported to give mixtures of isoflav-2-enes, isoflav-3-enes and isoflavans. The individual compounds are difficult to separate and can be obtained only in low yields. Sodium borohydride reductions of isoflavones are known, see Ádám Major *et al. Liebigs Ann. Chem.* (1988) 555-558, however the reactions are low yielding, typically not clean and substituents on the basic isoflavone ring structure require tedious protective groups not affected by metal hydrides.

Chromatography is often required to separate the reaction products and only low yields of isoflavanones, isoflavan-4-ols, isoflavenes and isoflavans are obtained. The chromatography required is tedious and often impracticable for large scale reactions. Furthermore, attempts to improve the yield and purity of products obtained from

hydrogenation reactions has been met with limited success as evidenced by published results which are largely contradictory.

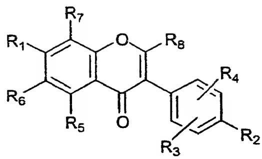
Solvents used in hydrogenation reactions of isoflavones reported in the literature include *N*-methylpyrrolidinone, see Liepa, A.J., *Aust. J. Chem.*, 1981, **34**, 2647-55. However this solvent is unsuitable for pharmaceutical preparations of isoflavone metabolites and derivatives because *N*-methylpyrrolidinone is a severe eye irritant and a possible carcinogen. Furthermore the high boiling point of the solvent makes it extremely difficult to remove after the reduction.

Isoflavan-4-ols are key intermediates in the synthesis of isoflavenes and accordingly there is a need for more efficient and reliable syntheses of isoflavan-4-ols, or at least comparable alternatives, acceptable than those known in the art. There is also a need for synthetic methods for isoflavone hydrogenation which utilise solvents pharmaceutically more acceptable than those previously reported. Therefore it is an object of the present invention to overcome or at least alleviate one or more of the above-mentioned disadvantages of the prior art. It is an other object of the present invention to synthesise novel isoflavone metabolites and derivatives.

Surprisingly hydrogenation conditions have been found by the present inventors which enable the synthesis of isoflavone derivatives in good to excellent yields. In particular the conditions found by the present inventors allow for the hydrogenation of isoflavones to relatively pure tetrahydroisoflavan-4-ol products in excellent yields, and without the need for pharmaceutically unsuitable solvents and extensive chromatography in the hydrogenation reactions.

Summary of the Invention

Thus the present invention provides a method for the hydrogenation of a compound of formula I



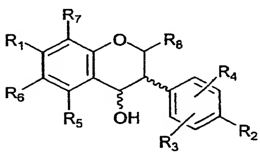
(I)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and

R_9 is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl,

to prepare a compound of formula II

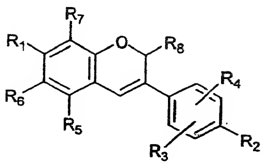


(II)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above.

The present invention also provides a method for the dehydration of a compound of formula II, which method may optionally include deprotection or transformation steps, to prepare a compound of the formula III



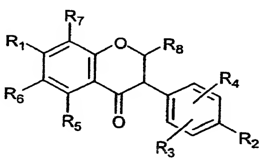
(III)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and

R_9 is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl.

The present invention also provides a method for the hydrogenation of a compound of formula I to prepare a compound of formula IV

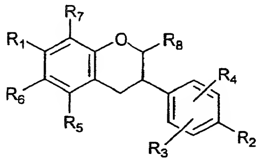


(IV)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above

The present invention also provides a method for the hydrogenation of a compound of formula III to prepare a compound of formula V



(V)

wherein
$R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8$ and R_9 are as defined above.

The present invention also provides compounds of formulae II, III, IV and V when prepared by a method described above and compositions comprising same.

The present invention also provides novel compounds of the formulae I, II, III, IV and V and compositions comprising same.

Detailed Description of the Invention

In the methods of the present invention, the starting isoflavone of formula I, the hydrogenation products isoflavan-4-ol of formula II, isoflavan-4-one of formula IV and isoflavan of formula V, and the dehydration product isoflav-3-ene of formula III preferably have the following substituents wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, aryl, arylalkyl, thio, alkylthio, bromo, chloro or fluoro, and

R_9 is alkyl, fluoroalkyl or arylalkyl;

more preferably they have the following substituents wherein

R_1 is hydroxy, OR_9 or $OC(O)R_9$,

R_2, R_3, R_4, R_5, R_6 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or arylalkyl,

R_8 is hydrogen, and

R_9 is methyl, ethyl, propyl, isopropyl or trifluoromethyl; and

most preferably they have the following substituents wherein

R_1 is hydroxy, OR_9 or $OC(O)R_9$,

R_2, R_3, R_4, R_5 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or arylalkyl,

R_6 and R_8 are hydrogen, and

R_9 is methyl.

The particularly preferred compounds of formula I are 4',7-diacetoxyisoflavone (daidzein diacetate) and 7-acetoxy-4'-methoxyisoflavone;

the particularly preferred compounds of formula II are 4',7-diacetoxyisoflavan-4-ol (tetrahydrodaidzein diacetate) and 7-acetoxy-4'-methoxyisoflavan-4-ol;

the particularly preferred compounds of formula III are 4',7-diacetoxyisoflav-3-ene (dehydroequol diacetate), 4',7-dihydroxyisoflav-3-ene (dehydroequol), 7-acetoxy-4'-methoxyisoflav-3-ene and 7-hydroxy-4'-methoxyisoflav-3-ene;

the particularly preferred compounds of formula IV are 4',7-diacetoxyisoflavan-4-one (diacetoxydihydrodaidzein) and 4',7-dihydroxyisoflavan-4-one (dihydrodaidzein); and

the particularly preferred compounds of formula V are 4',7-diacetoxyisoflavan (equol diacetate) and 4',7-dihydroxyisoflavan (equol).

The novel compounds of the formulae I, II, III, IV and V preferably have the following substituents wherein

R_1 is hydroxy, OR_9, $OC(O)R_9$, thio, alkylthio, or halo,

R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, aryl, thio, alkylthio or halo, and

R_9 is alkyl, fluoroalkyl or arylalkyl

with the proviso that

at least one of R_5, R_6 and R_7 is not hydrogen, or

when R_5, R_6 and R_7 are all hydrogen, then R_3 is hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, aryl, thio, alkylthio or halo; and

more preferably they have the following substituents wherein

R_1 is hydroxy, OR_9 or $OC(O)R_9$,

R_2 and R_3 are independently hydrogen, hydroxy, OR_9 or $OC(O)R_9$,

R_4, R_5, R_6, and R_8 are hydrogen,

R_7 is hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or halo, and

R_9 is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl; or wherein

R_1 is hydroxy, OR_9, $OC(O)R_9$,

R_2 and R_3 are independently hydrogen, hydroxy, OR_9 or $OC(O)R_9$,

R_5 is OR_9, $OC(O)R_9$, alkyl, aryl or halo,

R_4, R_6, R_7, and R_8 are hydrogen, and

R_9 is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl.

Most preferably the novel compounds of formulae I, II and III are:

4',7,8-Triacetoxyisoflavone
7,8-Diacetoxy-4'-methoxyisoflavone
4',7-Diacetoxy-8-methylisoflavone
3',7-Diacetoxy-8-methylisoflavone
7-Acetoxy-4'-methoxy-8-methylisoflavone
4',7-Diacetoxy-3'-methoxy-8-methylisoflavone
4',5,7-Triacetoxyisoflavone

4',7,8-Triacetoxyisoflavan-4-ol
7,8-Diacetoxy-4-methoxyisoflavan-4-ol
4',7-Diacetoxy-8-methylisoflavan-4-ol
3',7-Diacetoxy-8-methylisoflavan-4-ol
7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol
4',7-Diacetoxy-3'-methoxy-8-methylisoflavan-4-ol
4',5,7-Triacetoxyisoflavan-4-ol

4',7,8-Trihydroxyisoflavan-4-ol
7,8-Dihydroxy-4-methoxyisoflavan-4-ol
4',7-Dihydroxy-8-methylisoflavan-4-ol
3',7-Dihydroxy-8-methylisoflavan-4-ol
7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol

4',7-Dihydroxy-3'-methoxy-8-methylisoflavan-4-ol
4',5,7-Trihydroxyisoflavan-4-ol

4',7,8-Triacetoxydehydroequol (4',7,8-Triacetoxyisoflav-3-ene)
7,8-Diacetoxy-4-methoxydehydroequol (7,8-Diacetoxy-4-methoxyisoflav-3-ene)
4',7-Diacetoxy-8-methylisoflav-3-ene
3',7-Diacetoxy-8-methylisoflav-3-ene
7-Acetoxy-4'-methoxy-8-methylisoflav-3-ene
4',7-Diacetoxy-3'-methoxy-8-methylisoflav-3-ene
4',5,7-Triacetoxyisoflav-3-ene

Isoflav-3-ene-4',7,8-triol
4'-Methoxyisoflav-3-ene-7,8-diol
8-Methylisoflav-3-ene-4',7-diol
8-Methylisoflav-3-ene-3',7-diol
4'-Methoxy-8-methylisoflav-3-ene-7-ol
3'-Methoxy-8-methylisoflav-3-ene-4',7-diol
Isoflav-3-ene-4',5,7-triol

4',7-Dihydroxy-8-methylisoflavan-4-ol
7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol

The term "alkyl" is taken to mean both straight chain and branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tertiary butyl, and the like. Preferably the alkyl group is a lower alkyl of 1 to 6 carbon atoms. The alkyl group may optionally be substituted by one or more of fluorine, chlorine, bromine, iodine, carboxyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylamino-carbonyl, di-(C_1-C_4-alkyl)-amino-carbonyl, hydroxyl, C_1-C_4-alkoxy, formyloxy, C_1-C_4-alkyl-carbonyloxy, C_1-C_4-alkylthio, C_3-C_6-cylcoalkyl or phenyl.

The term "aryl" is taken to include phenyl and naphthyl and may be optionally substituted by one or more C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy, carbonyl, C_1-C_4-alkoxycarbonyl , C_1-C_4-alkylcarbonyloxy or halo.

The term "halo" is taken to mean one or more halogen radicals selected from fluoro, chloro, bromo, iodo and mixtures thereof, preferably fluoro and chloro, more preferably fluoro. Reference to for example "haloalkyl" includes monohalogenated, dihalogenated and up to perhalogenated alkyl groups. Preferred perhalogenated groups are trifluoromethyl and pentafluoroethyl.

The compounds of the invention include all salts, such as acid addition salts, anionic salts and zwitterionic salts, and in particular include pharmaceutically acceptable salts.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The hydrogenation is ideally preformed with hydrogen in the presence of a reduction catalyst and a solvent. The reaction is preferably conducted under hydrogen at a pressure of 1-20 atmospheres, more preferably 1-5 atmospheres. The reaction may be performed from 10 to 60°C and is typically carried out at room temperature.

The reaction time may range from 12 hours to 96 hours or more and is typically about 55 hours or more. Generally better yields and cleaner reactions are achieved with longer reaction times. It will be appreciated that reaction conditions may be varied depending on the individual nature of the compounds and the progress of the hydrogenation reaction.

The reduction catalysts may be selected from heterogeneous catalysts (whereby the catalyst is insoluble in the reaction medium) or homogenous catalysts (whereby the catalyst is soluble in the reaction medium). Examples of heterogeneous reduction catalysts include Raney nickel, palladium black, palladium hydroxide on carbon, palladium on activated carbon (1% Pd to 30% Pd), palladium on alumina powder, palladium on various barium salts, sodium borohydride reduced nickel, platinum metal, platinum black, platinum on activated carbon (1% Pt to 10% Pt), platinum oxide, rhodium salts, ruthenium salts and their chiral salts and zinc oxide. Preferably the catalyst is palladium on activated carbon (1% Pd

to 10% Pd), more preferably about 5% palladium on carbon. Platinum oxide (Adam's catalyst) is also a very useful hydrogenation catalyst for the methods of the present invention to produce predominantly *cis*-isomers of isoflavan-4-ols.

Examples of homogeneous reduction catalysts include chlorotris (triphenylphosphine)rhodium, chloro(trisphenylphosphine)hydridoruthenium (II) and pentacyanocobaltate (II).

The solvents suitable for use in the present invention include but are not limited to C_1-C_8 alcohols and polyols, alkyl acetates, tetrahydrofuran, ethers, dioxane and C_1-C_3 acids. Preferably the solvent is a C_1-C_6 alcohol or C_1-C_6 alkyl acetate, more preferably methanol, ethanol or ethyl actate, as well as propanol, isopropanol, butanol, isobutanol, secbutanol, tertiary butanol, methyl formate, ethyl formate and methly acetate. Most preferably the solvent is absolute methanol, ethanol or ethyl acetate.

The present inventors have found that with a judicious choice of catalysts, solvents and optionally protecting groups, isoflavones are reduced cleanly and in high yields to corresponding isoflavanols. In particular the use of absolute methanol or ethanol as a solvent provided for very clean catalytic hydrogenation over 5% palladium on charcoal of isoflavones to afford up to quantitative yields of isoflavanols. In methods where, for example, 10% palladium on charcoal is employed, the reaction can proceed more rapidly, at times being complete within 12 hours. The ratio of *cis*- and *trans*-isomers of the isoflavan-4-ol hydrogenation product can vary with the choice of catalysts and the nature of the isoflavone substitute. By varying the methods of the present invention it is possible to influence the isomeric ratio achieved during the reduction process.

Of particular interest are isoflavones with oxygen substitution (or precursors to oxygen substitution) at the 4'- and 7-positions as reduction of these compounds leads to the biologically important dehydroequol or precursors thereof. A convenient starting material is daidzein which is readily obtained by established routes.

It will be understood that some moieties on the isoflavone rings may require protection or derivatisation prior to being subjected to hydrogenation. For example it may be desirable to

protect free hydroxy moieties with groups such as an acetoxy group to assist in the solubility of the substituted isoflavones and/or their susceptibility to hydrogenation. Protecting groups can be carried out be well established methods known in the art, for example as described in *Protective Groups in Organic Synthesis,* T. W. Greene.

In particular the present inventors have found it is useful to protect hydroxy groups when present as esters or ethers prior to reduction, with acetoxy or methoxy groups most favoured. Acylation is preferably carried out with the hydroxy compounds in a solvent mixture of a carboxylic acid anhydride and base. Protecting free hydroxy groups prior to hydrogenation increases yields up to and including quantitative yields. The reaction products are generally cleaner and do not require a chromatography step in the purification and isolation of the hydrogenation products.

Thus surprisingly, tetrahydrodaidzein diacetate was obtained in quantitative yield when the catalytic hydrogenation of diacetoxydaidzein in ethanol was continued for 55 h. Spectroscopic analysis established the product to be a 1:1 mixture of *cis-* and *trans-*isomers. Pleasingly, no further reduction of tetrahydrodaidzein was observed even if the reduction was continued for longer periods of time.

In a similar manner it was also surprisingly found that the protected isoflavone 7-acetoxy-4'-methoxydaidzein smoothly and cleanly underwent hydrogenation in ethanol to afford a quantitative yield of a 1:1 mixture of *cis-* and *trans-*isomers of 7-acetoxy-4'-methoxyisoflavan-4-ol. This reaction appears to be quite general and was repeated on many different substrates in amounts of up to one half gram and more.

In this regard the inventors have found conditions which allow for the large scale generation of clean and near quantitative yields of isoflavan-4-ols compounds by hydrogenation of corresponding isoflavones. In particular, it has been found that kilogram quantities of diacetoxy daidzein undergo smooth and efficient reduction to the isomeric *cis-* and *trans-* 4',7-diacetoxyisoflavan-4-ols. The isomeric ratios can be influenced by the percentage of palladium in the catalyst.

The *cis-/trans*-isomeric mixtures are able to be dehydrated to isoflav-3-enes without the need for separation. However, is desired, the mixtures are able to be separated by a variety of methods as set out below.

The mixture of *cis*- and *trans*-tetrahydrodaidzein compounds are able to be separated by preparative HPLC. This mode of separation is quite tedious and limited to small amounts of material. Since reasonable quantities of the diacetoxy isoflavanols were able to be prepared, fractional crystallisation was attempted to separate the *cis*- and *trans*-isomers. A single recrystallisation of the 1:1 mixture from ethanol gave predominantly *trans*-diacetoxytetrahydrodaidzein (50% yield: 73% purity) (*cis*-isomer 27%). Subsequent recrystallisations from ethanol afforded the pure *trans*- isomer in 25% overall yield.

Likewise the 7-acetoxy-4'-methoxyisoflavan-4-ol was able to be fractionally recrystallised to give the pure *trans*-isomer, with the filtrate containing increased proportions of the *cis*-isomer.

Most hydrogenations yielded 1:1 mixtures of *cis*- and *trans*-isoflavan-4-ols. However one derivative of note was 7-hydroxy-4'-methoxy-8-methylisoflavone, the hydrogenation of which afforded predominantly the *trans*- isomer in excellent yield.

Synthesis of tetrahydrodaidzein and related derivatives was achieved by removal of the protecting acetoxy groups under mild conditions, preferably with imidazole in ethanol at reflux. Tetrahydrodaidzein was isolated in 80% yield after crystallisation from aqueous ethanol.

Dehydration of isoflavan-4-ols leads to the unsaturated isoflav-3-enes. Thus reaction of a *cis-/trans*-mixture of isoflavan-4-ols with benzoyl chloride/dimethylformamide at 100°C has been reported in the literature by Liepa to give the desired isoflav-3-ene dehydration product. However this reaction could only be repeated in low yield. Dehydration may also be effected by treatment with acids such as sulfuric acid, hydrochloric acid, polyphosphoric acid, thionyl chloride and the like. Alternative methods of dehydration using *p*-toluenesulfonic acid or trifluoroacetic acid in refluxing dichloromethane were also investigated, but these methods also afforded the isoflavenes in low yields.

Generally the present inventors found the dehydration reagent of choice to be phosphorus pentoxide in dichloromethane, which can yield isoflavenes in yields of greater than 60%. The dehydration reactions can be carried out on the hydrogenation products directly, or deprotected derivatives thereof.

Synthesis of dehydroequol was achieved by removal of the protecting acetoxy groups under mild conditions as described for the synthesis of tetrahydrodaidzein, and dehydroequol was purified by standard crystallisation solvent mixtures such as ethanol/water. Other isoflav-3-ene derivatives may be prepared by similar methods.

Hydrogen reduction of 4',7-diacetoxydaidzein with Adam's catalyst (platinum(IV)oxide) in ethyl acetate under an atmosphere of hydrogen afforded 4',7-diacetoxytetrahydrodaidzein. However unlike the palladium-on-charcoal reduction in ethanol, reductions with Adam's catalyst gave predominantly the *cis*-isomer of 4',7-diacetoxytetrahydrodaidzein.

In another embodiment of the invention, hydrogenation of 4',7-diacetoxy daidzein with 5% palladium-on-charcoal in ethyl acetate as solvent under an atmosphere of hydrogen gave 4',7-diacetoxydihydrodaidzein in excellent yield (80%). These conditions provide access to isoflavan-4-ones from the corresponding isoflavones in good to excellent yields.

Access to isoflavan derivatives such as equol is possible by hydrogenation of isoflav-3-enes with, preferably, palladium-on-charcoal in an alkyl acetate solvent under an atmosphere of hydrogen. Excellent yields of 75% and more of the hydrogenated products are obtainable by these methods. The products are clean and are readily recrystallised.

The surprising results obtained by the present inventors are in sharp contrast to those reported in the literature for other attempted hydrogenations of isoflavones. One such marked advantage is the use of alkyl acetates or alcohol solvents such as absolute methanol or ethanol in the hydrogenation reactions. The isoflavanols prepared by the methods of the present invention are typically very crystalline and can be isolated in good purity, and without the need for chromatography. The isoflavanols can be converted to isoflav-3-enes by dehydration. Further deprotection or derivatisation steps can be employed by those

skilled in the art to obtain natural isoflavan-4-ones, isoflavans, isoflavenes, metabolites and novel derivatives thereof as required.

The invention is further described in and illustrated by the following Examples. The Examples are not to be construed as limiting the invention in any way.

EXAMPLES

Acetylation Reactions

Example 1

4',7 Diacetoxydaidzein

Method A

A mixture of daidzein (1.0g, 3.9 mmol), acetic anhydride (5 ml) and pyridine (5 ml) was left in the dark at room temperature for 24 h. The reaction mixture was poured into water (100 ml), stirred for 2h and then extracted with dichloromethane (3 x 50 ml). The dichloromethane layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The white residue was crystallised from methanol to yield daidzein diacetate as white prisms (1.1 g, 83%). ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, $OCOCH_3$), 2.36 (s, 3H, $OCOCH_3$), 7.18 (d, 2H, J 9.2 Hz, ArH), 7.19 (d, 1H, J 9.0 Hz, H6), 7.31 (d, 1H, J 2.0 Hz H8), 7.59 (d, 2H, J 9.2 Hz, ArH), 8.00 (s, 1H, H2), 8.33 (d, 2H, J 8.2 Hz, ArH).

Method B

A mixture of daidzein (2.0 g, 7.9 mmol), acetic anhydride (10 ml) and pyridine (2 ml) was heated on an oil bath at 105-110 C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with water and recrystallised from methanol to yield daidzein diacetate as colourless prisms (2.4 g, 90%).

Example 2

7-acetoxy-4'-methoxyisoflavone

A mixture of 7-hydroxy-4'-methoxyisoflavanone (2.0g, 7.5 mmol), acetic anhydride (10 ml) and pyridine (2 ml) was heated on an oil bath at 105-110 C for 1 hour. After cooling the

mixture to room temperature, it was poured into water (100 ml), stirred for 2 hours and then extracted with dichloromethane (3 x 50 ml). The dichloromethane layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The white residue was crystallised from methanol to yield 7-acetoxy-4'-methoxyisoflavone as colourless prisms (2.1g, 91%). ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, $OCOCH_3$), 3.84 (s, 3H, OCH_3), 6.98 (d, 2H, J 8.7 Hz, ArH), 7.16 (dd, 1H, J 1.9 Hz 8.6 Hz, H6), 7.30 (d, 1H, J 1.9 Hz H8), 7.50 (d, 2H, J 8.7 Hz, ArH), 8.00 (s, 1H, H2), 8.32 (d, 1H, J 8.6 Hz, H5).

Example 3

3',7-Diacetoxyisoflavone

3',7-Diacetoxydaidzein was prepared from 3',7-dihydroxyisoflavone (0.98g, 3.9 mmol), acetic anhydride (6 ml) and pyridine (1.1 ml) as described for 4',7-diacetoxydaidzein. Yield: (1.0g, 77%) m.p. 152°C. ^{1}H NMR ($CDCl_3$): δ 2.31 and 2.36 (each s, 3H, $OCOCH_3$), 7.14 (m, 1H, ArH), 7.18 (dd, 1H, J 2.0 Hz 8.6 Hz, H6), 7.31 (d, 1H, J 2.0 Hz H8), 7.37-7.45 (m, 3H, ArH), 8.03 (s, 1H, H2), 8.32 (d, 1H, J 8.6 Hz, H5). Mass spectrum: m/z 338 (M, 8%); 296 (53); 254 (100); 253 (60).

Example 4

7-Acetoxy-3'-methoxyisoflavone

7-Acetoxy-3'-methoxyisoflavone was prepared from 7-hydroxy-3'-methoxyisoflavone (1.7g, 6.3 mmol), acetic anhydride (6 ml) and pyridine (1.0 ml) as described for 4',7-diacetoxydaidzein. Yield: (1.6g, 81%) m.p. 118°C. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, $OCOCH_3$), 3.85 (s, 3H, OMe), 6.95 (dd, 1H, J 2.0 Hz 8.3 Hz, H6), 6.70-7.40 (m, 5H, ArH), 8.01 (s, 1H, H2), 8.32 (d, 1H, J 8.7 Hz, H5).

Example 5

4',7-Diacetoxy-3'-methoxyisoflavone

4',7-Diacetoxy-3'-methoxyisoflavone was prepared from 4',7-dihydroxy-3'-methoxyisoflavone (0.37g, 1.3 mmol), acetic anhydride (2.5 ml) and pyridine (0.4 ml) as described for 4',7-diacetoxydaidzein. Yield: (0.36g, 75%) m.p. 197°C. ^{1}H NMR ($CDCl_3$): δ 2.33, 2.36 (each s, 3H, $OCOCH_3$), 3.88 (s, 3H, OMe), 7.06-7.17 (m, 2H, ArH), 7.19 (dd,

1H, J 2.3 Hz 9.0 Hz, ArH), 7.32 (dd, 2H, J 2.3 Hz 7.6 Hz, ArH), 8.03 (s, 1H, H2), 8.32 (d, 1H, J 8.6 Hz, H5).

Example 6

7-Acetoxyisoflavone

7-Acetoxyisoflavone was prepared from 7-hydroxyisoflavone (2.6g, 10.9 mmol), acetic anhydride (16 ml) and pyridine (3.0 ml) as described for 4',7-diacetoxydaidzein. Yield: (2.5g, 82%) m.p. 133°C. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, $OCOCH_3$), 7.18 (dd, 1H, J 2.2 Hz 8.6 Hz, H6), 7.31 (d, 1H, J 2.2 Hz H8), 7.39-7.57 (m, 5H, ArH), 8.00 (s, 1H, H2), 8.33 (d, 1H, J 8.6 Hz, H5). Mass spectrum: m/z 280 (M, 28%); 237 (98); 238 (57).

Example 7

4',7,8-Triacetoxyisoflavone

A mixture of 4',7,8-trihydroxyisoflavone (1.4g, 5.2 mmol), acetic anhydride (8.4 ml) and pyridine (2 ml) was heated on an oil bath at 105-110°C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with water and recrystallised from ethyl acetate to yield 4',7,8-triacetoxyisoflavone as colourless prisms (1.49g, 73%) m.p. 190-192°C. ^{1}H NMR ($CDCl_3$): δ 2.32, 2.36, 2.42 (each s, 3H, $OCOCH_3$), 7.18 (d, 2H, J 8.6 Hz, ArH), 7.28 (d, 1H, J 8.9 Hz, H6), 7.56 (d, 2H, J 8.6 Hz H8), 7.98 (s, 1H, ArH), 8.18 (d, 1H, J 8.9 Hz, H5).

Example 8

7,8-Diacetoxy-4'-methoxyisoflavone

7,8-Diacetoxy-4'-methoxyisoflavone was prepared from 7,8-dihydroxy-4'-methoxyisoflavone (0.82g, 2.9 mmol), acetic anhydride (4.9 ml) and pyridine (0.9 ml) as described for 4',7,8-triacetoxyisoflavone. Yield: (0.9g, 85%) m.p. 165°C. ^{1}H NMR ($CDCl_3$): δ 2.36, 2.42 (each s, 3H, $OCOCH_3$), 3.84 (s, 3H, OCH_3), 6.98 (d, 2H, J 9.0 Hz, ArH), 7.25 (d, 1H, J 8.7 Hz, H6), 7.48 (d, 2H, J 9.0 Hz H8), 7.95 (s, 1H, H2), 8.20 (d, 1H, J 9.1 Hz, H5). Mass spectrum: m/z 368 (M, 20%); 326 (15); 312 (18); 284 (80).

Example 9

4',7-Diacetoxy-8-methylisoflavone

A mixture of 4',7-dihydroxy-8-methylisoflavone (2.9g, 10.8 mmol), acetic anhydride (18 ml) and pyridine (3 ml) was heated on an oil bath at 105-110°C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with water and recrystallised from ethyl acetate to yield 4',7-diacetoxy-8-methylisoflavone as colourless prisms (3.2g, 84%). ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.32, 2.39 (each s, 3H, $OCOCH_3$), 7.13 (d, 1H, J 9.0 Hz, H6), 7.17 (d, 2H, J 8.7 Hz, ArH), 7.59 (d, 2H, J 8.7 Hz, ArH), 8.07 (s, 1H, H2), 8.19 (d, 1H, J 8.7 Hz, H5).

Example 10

3',7-Diacetoxy-8-methylisoflavone

3',7-Diacetoxy-8-methylisoflavone was prepared from 3',7-dihydroxy-8-methylisoflavone (1.3g, 4.8 mmol), acetic anhydride (8 ml) and pyridine (1.5 ml) as described for 4',7-diacetoxy-8-methylisoflavone. Yield: (1.2g, 70%) m.p. 112°C. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.32, 2.39 (each s, 3H, $OCOCH_3$), 7.13 (m, 2H, ArH), 7.37-7.45 (m, 3H, ArH), 8.1 (s, 1H, H2), 8.18 (d, 1H, J 8.7 Hz, H5). Mass spectrum: m/z 352 (M, 6%); 310 (35); 268 (100); 267 (60).

Example 11

7-Acetoxy-4'-methoxy-8-methylisoflavone

7-Acetoxy-4'-methoxy-8-methylisoflavone was prepared from 7-hydroxy-4'-methoxy-8-methylisoflavanone (3.0g, 10.6 mmol), acetic anhydride (10 ml) and pyridine (2.0 ml) as described for 4',7-diacetoxy-8-methylisoflavone. Yield: (2.0g, 58%) m.p. 190-192°C. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.38 (s, 3H, $OCOCH_3$), 3.84 (s, 3H, OMe), 6.98 (d, 2H, J 8.7 Hz, ArH), 7.12 (d, 1H, J 8.6 Hz, H6), 7.52 (d, 2H, J 8.7 Hz, ArH), 8.03 (s, 1H, H2), 8.18 (d, 1H, J 8.6 Hz, H5). Mass spectrum: 325 (M + 1, 13%); 324 (M, 58%); 282 (100); 281 (42).

Example 12

4',7-Diacetoxy-3'-methoxy-8-methylisoflavone

4',7-Diacetoxy-3'-methoxy-8-methylisoflavone was prepared from 4',7-dihydroxy-3'-methoxy-8-methylisoflavone (0.42g, 1.4 mmol), acetic anhydride (2.6 ml) and pyridine (0.5 ml) as described for 4',7-diacetoxy-8-methylisoflavone. Yield: (0.4g, 74%) m.p. 209°C. ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H, CH_3), 2.32, 2.39 (each s, 3H, $OCOCH_3$), 3.89 (s, 3H, OMe), 7.07-7.11 (m, 2H, ArH), 7.13 (d, 1H, J 8.6 Hz, H6), 7.32 (d, 1H, J 1.5 Hz, ArH), 8.09 (s, 1H, H2), 8.18 (d, 1H, J 8.7 Hz, H5).

Hydrogenation Reactions:- Isoflavone → Isoflavan-4-ol

Example 13

4',7-diacetoxytetrahydrodaidzein (4'7-Diacetoxyisoflavan-4-ol)

Method A

Palladium-on-charcoal (5%, 0.08 g) was added to a suspension of 4',7-diacetoxydaidzein (0.5 g, 1.5 mmol) in absolute ethanol (400 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55 hours. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 4',7-diacetoxytetrahydrodaidzein (0.51 g, 100%) in quantitative yield. A nuclear magnetic resonance spectrum revealed the product to be a clean 1:1 mixture of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein.

The *cis*- and *trans*-isomers were able to be separated by fractional recrystallisation. A 1:1 mixture of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein (0.17 g), prepared as above, was dissolved in excess absolute ethanol and concentrated on a rotary evaporator. At the first sign of crystallisation, further concentration of ethanol was stopped and the flask was cooled in an ice-bath. The resulting crystals were filtered and washed with a small amount of cold absolute ethanol. A nuclear magnetic resonance spectrum of the product (0.08 g) revealed it to be a mixture *trans*-4',7-diacetoxytetrahydrodaidzein (73%) and *cis*-4',7-diacetoxytetrahydrodaidzein (27%). Further recrystallisations of the mixture from ethanol yielded the pure *trans*-4',7-diacetoxytetrahydrodaidzein (0.04 g, 24%).

The filtrate yielded predominantly *cis*-isomer. Nuclear magnetic resonance spectroscopic analysis revealed the substance to be a mixture of *cis*-4',7-diacetoxytetrahydrodaidzein (73%) and *trans*-4',7-diacetoxytetrahydrodaidzein (27%).

For *trans*-4',7-Diacetoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, $OCOCH_3$), 2.29 (s, 3H $OCOCH_3$), 3.14 (ddd, 1H, J 3.7 Hz, 7.9 Hz, 9.1 Hz, H3), 4.24 (dd, 1H, J 9.1 Hz, 11.3 Hz, H2); 4.35 (dd, 1H, J 3.7 Hz, 11.3 Hz, H2), 4.87 (d, 1H, J 7.9 Hz, H4), 6.61 (d, 1H, J 2.3 Hz, H8), 6.70 (dd, 1H, J 2.3 Hz, 8.4 Hz, H6), 7.06 (d, 2H, J 8.6 Hz, ArH), 7.23 (d, 2H, J 8.4 Hz, ArH), 7.44 (dd, 1H, J 0.8 Hz, 8.4 Hz, H5). ^{13}C NMR ($CDCl_3$): 20.98 ($OCOCH_3$), 46.18 (C3), 68.04 (C2), 69.01 (C4), 109.67 (C8), 114.26 (C6), 121.96, 128.96 (ArCH), 129.40 (C5).

For *cis*-4',7-Diacetoxyisoflavan-4-ol: ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, $OCOCH_3$), 2.29 (s, 3H, $OCOCH_3$), 3.30 (dt, 1H, J 3.4 Hz, J 11.8 Hz, H3), 4.31 (ddd, 1H, J 1.4 Hz, 3.6 Hz, 10.5 Hz, H2); 4.56 (dd, 1H, J 10.5 Hz, 11.8 Hz, H2), 4.75 (dd, 1H, J 1.3 Hz, 3.2 Hz, H4), 6.66 (dd, 1H, J 2.3 Hz, 8.7 Hz, H6), 6.69 (d, 1H, J 2.3 Hz, H8), 7.08 (d, 2H, J 8.6 Hz, ArH), 7.26 (d, 1H, 8.4 Hz, H5), 7.29 (d, 2H, J 8.6 Hz ArH). ^{13}C NMR ($CDCl_3$); 20.98 ($OCOCH_3$), 43.52 (C3), 64.10 (C2), 66.46 (C4), 110.08 (C6), 114.09 (C8), 121.82, 129.40 (ArCH), 131.10 (C5).

Method B

Palladium-on-charcoal (5%, 3.1 g) was added to a suspension of 4',7-diacetoxydaidzein (30.0 g) in absolute methanol (3600 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55 hours. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 4',7-diacetoxytetrahydrodaidzein (29.5g, 96%). A nuclear magnetic resonance spectrum revealed the product to be a clean 2:1 mixture of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein.

Method C

Palladium-on-charcoal (10%, 3.0 g) was added to a suspension of 4',7-diacetoxydaidzein (30.1g) in absolute methanol (3600 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 15 hours. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 4',7-diacetoxytetrahydrodaidzein

(28.5g, 94%). A nuclear magnetic resonance spectrum revealed the product to be a clean 1:1 mixture of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein.

Method D

Palladium-on-charcoal (5%, 100g) was added to a suspension of 4',7-diacetoxydaidzein (980g) in absolute methanol (100L) and the mixture was stirred at room temperature under a hydrogen atmosphere for 78 hours. The catalyst was removed by filtration through a ceramic candle filtratation apparatus and the filtrate was evaporated *in vacuo* to yield 4',7-diacetoxytetrahydrodaidzein (820g, 83%). A nuclear magnetic resonance spectrum revealed the product to be a clean 2:1 mixture of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein.

Example 14

Synthesis of 7-Acetoxy-4'-methoxyisoflavan-4-ol

Palladium-on-charcoal (5%, 0.08g) was added to a suspension of 7-acetoxy-4'-methoxyisoflavone (0.5g, 1.6 mmol) in absolute ethanol (400 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55 hours. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 7-acetoxy-4'-methoxyisoflavan-4-ol (0.51g, 100%) in quantitative yield. A nuclear magnetic resonance spectrum revealed the product to be a clean 1:1 mixture of *cis*- and *trans*-7-acetoxy-4'-methoxyisoflavan-4-ol.

The *cis*- and *trans*-isomers were able to be separated by fractional recrystallisation. A 1:1 mixture of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein, prepared as above, was recrystallised three times from ethanol to yield pure *trans*-7-acetoxy-4'-methoxyisoflavan-4-ol. The filtrate yielded predominantly *cis*-isomer.

For *trans*-7-Acetoxy-4'-methoxyisoflavan-4-ol; 1H NMR ($CDC1_3$): δ 2.31 (s, 3H, $OCOCH_3$), 3.14 (dt, 1H, J 3.8 Hz, 8.6 Hz, H3), 3.82 (s, 3H, OCH_3), 4.25 (dd, 1H, J 9.4 Hz, 11.3 Hz, H2); 4.37 (dd, 1H, J 4.1 Hz, 11.3 Hz, H2), 4.93 (d, 1H, J 7.8 Hz, H4), 6.63 (d, 1H, J 2.3 Hz, H8), 6.73 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.93 (d, 2H, J 8.7 Hz, ArH), 7.19 (d, 2H, J 8.7 Hz, ArH), 7.51 (d, 1H, J 7.9 Hz, H5).

For *cis*-7-Acetoxy-4'-methoxyisoflavan-4-ol; 1H NMR ($CDC1_3$): δ 2.30 (s, 3H, $OCOCH_3$), 3.28 (dt, 1H, J 3.4 Hz, J 12.1 Hz, H3), 3.84 (s, 3H, OCH3), 4.36 (ddd, 1H, J 1.4 Hz, 3.8 Hz, 10.1 Hz, H2); 4.57 (dd, 1H, J 10.1 Hz, 11.3 Hz, H2), 4.75 (bs, 1H, H4), 6.58 (d, 1H, J 2.3 Hz, H8), 6.75 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.96 (d, 2H, J 8.6 Hz, ArH), 7.25 (d, 2H, 8.6 Hz, ArH), 7.34 (d, 1H, J 8.3 Hz, H5).

Example 15

3'-7-Diacetoxyisoflavan-4-ol

Palladium-on-charcoal (5%, 0.03g) was added to a suspension of 3',7-diacetoxyisoflavanone (0.2g, 0.6 mmol) in methanol (50 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55h. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 3'-7-diacetoxyisoflavan-4-ol in quantitative yield. A nuclear magnetic resonance spectrum revealed the product to be a clean 1 : 1 mixture of *cis*- and *trans*-3'-7-diacetoxyisoflavan-4-ol.

For *trans*-3'-7-diacetoxyisoflavan-4-ol; ^1H NMR ($CDCl_3$): δ 2.31 and 2.32 (each s, 3H, $OCOCH_3$), 3.17 (ddd, 1H, J 3.6 Hz, 8.6 Hz, 11.2 Hz, H3), 4.26 (dd, 1H, J 9.2 Hz, 11.6 Hz, H2); 4.33 (m, 1H, H2), 4.91 (d, 1H, J 7.9 Hz, H4), 6.60-6.73 (m, ArH), 6.97-7.16 (m, ArH), 7.25-7.48 (m, ArH).

For *cis*-3'-7-diacetoxyisoflavan-4-ol; ^1H NMR ($CDCl_3$): δ 2.30 and 2.31 (each s, 3H, $OCOCH_3$), 3.31 (dt, 1H, J 3.3 Hz, J 11.6 Hz, H3), 4.31 (m, 1H, H2); 4.57 (dd, 1H, J 10.6 Hz, 11.9 Hz, H2), 4.79 (bs, 1H, H4), 6.60-6.73 (m, ArH), 6.97-7.16 (m, ArH), 7.25-7.48 (m, ArH).

Example 16

7-Acetoxy-3'-methoxyisoflavan-4-ol

Cis- and *trans*-7-acetoxy-3'-methoxyisoflavan-4-ol was prepared from 7-acetoxy-3'-methoxyisoflavone (0.5g, 1.6 mmol) and palladium-on-charcoal (5%, 0.12g) in methanol (100 ml) by the method described above.

For *trans*-7-acetoxy-3'-methoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, $OCOCH_3$), 3.15 (ddd, 1H, J 3.8 Hz, 8.3 Hz, 12.0 Hz, H3), 3.80 (s, 3H, OMe), 4.26 (dd, 1H, J 9.4 Hz, 11.3 Hz, H2); 4.32 (m, 1H, H2), 4.95 (d, 1H, J 7.9 Hz, H4), 6.60-6.93 (m, ArH), 7.23-7.33 (m, ArH), 7.49 (d, J 8.7 Hz, ArH).

For *cis*-7-acetoxy-3'-methoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, $OCOCH_3$), 3.30 (dt, 1H, J 3.3 Hz, J 11.7 Hz, H3), 4.31 (m, 1H, H2); 4.58 (dd, 1H, J 10.5 Hz, 11.7 Hz, H2), 4.81 (bs, 1H, H4), 6.60-6.93 (m, ArH), 7.23-7.33 (m, ArH), 7.49 (d, J 8.7 Hz, ArH).

Example 17

4',7-Diacetoxy-3'-methoxyisoflavan-4-ol

Cis- and *trans*-4'-7-diacetoxy-3'-methoxyisoflavan-4-ol was prepared from 4'-7-diacetoxy-3'-methoxyisoflavone (0.25g, 0.7 mmol) and palladium-on-charcoal (5%, 0.06g) in methanol (50 ml) by the method described above.

For *trans*-4'-7-diacetoxy-3'-methoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.29, 2.31 (each s, 3H, $OCOCH_3$), 3.17 (ddd, 1H, J 3.8 Hz, 8.7 Hz, 12.5 Hz, H3), 3.79 (s, 3H, OMe), 4.26 (dd, 1H, J 9.4 Hz, 11.3 Hz, H2); 4.32 (m, 1H, H2), 4.93 (d, 1H, J 7.9 Hz, H4), 6.62-6.73 (m, ArH), 6.81-6.91 (m, ArH), 6.99-7.05 (m, ArH), 7.30 (d, J 8.3 Hz, ArH), 7.48 (d, J 9.0 Hz, ArH).

For *cis*-7-acetoxy-3'-methoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.31,2.32 (each s, 3H, $OCOCH_3$), 3.33 (dt, 1H, J 3.3 Hz, J 11.3 Hz, H3), 3.83 (s, 3H, OMe), 4.31 (m, 1H, H2); 4.58 (t, 1H, J 10.5 Hz, H2), 4.82 (bs, 1H, H4), 6.62-6.73 (m, ArH), 6.81-6.91 (m, ArH), 6.99-7.05 (m, ArH), 7.30 (d, J 8.3 Hz, ArH), 7.48 (d, J 9.0 Hz, ArH).

Example 18

7-Acetoxyisoflavan-4-ol

Cis- and *trans*-7-acetoxyisoflavan-4-ol was prepared from 7-acetoxyisoflavone (0.4g, 1.4 mmol) and palladium-on-charcoal (5%, 0.09g) in absolute methanol (60 ml). m.p. 90°C. Mass spectrum: m/z 284 (M, 10%); 226 (42); 138 (100); 137 (58).

For *trans*-7-acetoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, $OCOCH_3$), 3.17 (m, 1H, H3), 4.27 (t, 1H, J 10.6 Hz, H2); 4.30 (m, 1H, H2), 4.97 (d, 1H, J 8.3 Hz, H4), 6.60-6.73 (m, ArH), 7.08 (d, J 8.7 Hz, ArH), 7.23-7.37 (m, ArH), 7.49 (d, J 8.7 Hz, ArH).

For *cis*-7-acetoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H, $OCOCH_3$), 3.33 (dt, 1H, J 3.4 Hz, J 11.7 Hz, H3), 4.36 (m, 1H, H2); 4.62 (t, 1H, J 10.5 Hz, H2), 4.80 (bs, 1H, H4), 6.60-6.73 (m, ArH), 7.08 (d, J 8.7 Hz, ArH), 7.23-7.37 (m, ArH), 7.49 (d, J 8.7 Hz, ArH).

Example 19

4',7,8-Triacetoxyisoflavan-4-ol

Palladium-on-charcoal (5%, 0.07g) was added to a suspension of 4',7,8-triacetoxyisoflavone (0.5g, 1.3 mmol) in methanol (100 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55h. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 4',7,8-triacetoxyisoflavan-4-ol in quantitative yield. A nuclear magnetic resonance spectrum revealed the product to be a clean 1:1 mixture of *cis*- and *trans*-4',7,8-triacetoxyisoflavan-4-ol. Mass spectrum: m/z 400 (M, 5%); 358 (12); 298 (12); 256 (24); 196 (20); 162 (70); 154 (100); 120 (80).

For *trans*-4',7,8-triacetoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.28, 2.29. 2.31 (each s, 3H, $OCOCH_3$), 3.20 (m, 1H, H3), 4.27 (dd, 1H, H2); 4.37 (m, 1H, H2), 4.93 (d, 1H, J 7.9 Hz, H4), 6.78 (d, 1H, J 8.3 Hz, H8), 7.09 (m, ArH), 7.11-7.31 (m, ArH), 7.39 (d, 1H, J 8.7 Hz, ArH).

For *cis*-4',7,8-triacetoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.30, 2.31, 2.32 (each s, 3H, $OCOCH_3$), 3.35 (m, 1H, H3), 4.38 (m, 1H, H2); 4.57 (t, 1H, J 10.6 Hz, H2), 4.75 (bs, 1H, H4), 6.78 (d, 1H, J 8.3 Hz, H8), 7.09 (m, ArH), 7.11-7.31 (m, ArH), 7.39 (d, 1H, J 8.7 Hz, ArH).

Example 20

7,8-Diacetoxy-4-methoxyisoflavan-4-ol

7,8-Diacetoxy-4-methoxyisoflavan-4-ol was prepared from 7,8-dihydroxy-4'-methoxyisoflavone (0.4g, 1.1 mmol) in methanol (120 ml) using palladium-on-charcoal (5%, 0.08g) by the method described above.

For *trans*-7,8-diacetoxy-4-methoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.29, 2.30 (each s, 3H, $OCOCH_3$), 3.14 (ddd, 1H, J 3.9 Hz, 9.2Hz, 12.5 Hz, H3), 3.79 (s, 3H, OCH_3), 4.24 (dd, 1H, J 9.6 Hz, 11.2 Hz, H2); 4.35 (m, 1H, H2), 4.92 (d, 1H, J 7.8 Hz, H4), 6.78 (d, 1H, J 8.6 Hz, H6), 6.90 (m, ArH), 7.13-7.22 (m, ArH), 7.38 (d, J 8.6 Hz, ArH).

For *cis*-7,8-diacetoxy-4-methoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.30, 2.31 (each s, 3H, $OCOCH_3$), 3.29 (dt, 1H, J 3.0 Hz, J 12.0 Hz, H3), 3.80 (s, 3H, OCH_3), 4.36 (m, 1H, H2); 4.57 (t, 1H, J 10.6 Hz, H2), 4.75 (bs, 1H, H4), 6.77 (d, 1H, J 8.6 Hz, H6), 6.90 (m, ArH), 7.13-7.22 (m, ArH), 7.38 (d, J 8.6 Hz, ArH).

Example 21

4',7-Diacetoxy-8-methylisoflavan-4-ol

Palladium-on-charcoal (5%, 0.12g) was added to a suspension of 4',7-diacetoxy-8-methylisoflavone (1.0g, 2.8 mmol) in methanol (200 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55h. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield 4',7-diacetoxy-8-methylisoflavan-4-ol in quantitative yield, m.p. 135-37°C. A nuclear magnetic resonance spectrum revealed the product to be a clean 1:1 mixture of *cis*- and *trans*-4',7-diacetoxy-8-methylisoflavan-4-ol. Mass spectrum: 356 (M, 53%); 254 (86); 253 (100); 240 (80); 196 (37).

For *trans*-4',7-diacetoxy-8-methylisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3H, CH_3), 2.30, 2.31 (each s, 3H, $OCOCH_3$), 3.15 (ddd, 1H, J 3.8 Hz, 8.6 Hz, 11.7, H3), 4.27 (dd, 1H, J 9.4 Hz, 11.3 Hz, H2); 4.39 (m, 1H, H2), 4.92 (d, 1H, J 7.5 Hz, H4), 6.64 (d, 1H, J 8.0 Hz, H6), 7.06-7.32 (m, ArH).

For *cis*-4',7-diacetoxy-8-methylisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3H, CH_3), 2.31, 2.32 (each s, 3H, $OCOCH_3$), 3.28 (dt, 1H, J 3.4 Hz, J 11.7 Hz, H3), 4.40 (m, 1H, H2); 4.58

(dd, 1H, J 10.1 Hz, 11.7 Hz, H2), 4.78 (bs, 1H, H4), 6.67 (d, 1H, J 8.0 Hz, H6), 7.06-7.32 (m, ArH).

Example 22

3',7-Diacetoxy-8-methylisoflavan-4-ol

3',7-Diacetoxy-8-methylisoflavan-4-ol was prepared from 3',7-diacetoxy-8-methylisoflavone (0.25g, 0.7 mmol) in methanol (50 ml) using palladium-on-charcoal (5%, 0.06g) by the method described above.

For *trans*-3',7-diacetoxy-8-methylisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.03 (s, 3H, CH_3), 2.30, 2.32 (each s, 3H, $OCOCH_3$), 3.18 (ddd, 1H, J 3.8 Hz, 8.3 Hz, 12.1 Hz, H3), 4.28 (dd, 1H, J 9.0 Hz, 10.9 Hz, H2); 4.39 (m, 1H, H2), 4.94 (d, 1H, J 8.7 Hz, H4), 6.65 (d, 1H, J 7.9 Hz, H6), 6.98-7.39 (m, ArH).

For *cis*-3',7-diacetoxy-8-methylisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H, CH_3), 2.30, 2.32 (each s, 3H, $OCOCH_3$), 3.32 (dt, 1H, J 3.4 Hz, J 12.0 Hz, H3), 4.39 (m, 1H, H2); 4.59 (dd, 1H, J 10.5 Hz, 11.7 Hz, H2), 4.80 (bs, 1H, H4), 6.68 (d, 1H, J 8.3 Hz, H6), 6.98-7.39 (m, ArH).

Example 23

7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol

7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol was prepared from 7-hydroxy-4'-methoxy-8-methylisoflavone (0.25g, 0.8 mmol) in methanol (50 ml) using palladium-on-charcoal (5%, 0.08g) by the method described above. This hydrogenation reaction predominantly yielded the *trans*-isomer.

For *trans*-7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3H, CH_3), 2.32 (s, 3H, $OCOCH_3$), 3.11 (ddd, 1H, J 3.8 Hz, 9.4 Hz, 12.1 Hz, H3), 3.80 (s, 3H, OMe), 4.25 (dd, 1H, J 9.4 Hz, 11.3 Hz, H2); 4.40 (dd, 1H, J 3.8 Hz, 12.6 Hz, H2), 4.92 (bd, 1H, H4), 6.67 (d, 1H, J 8.3 Hz, H6), 6.89 (d, 2H, J 8.7 Hz, ArH), 7.16 (d, 2H, J 8.7 Hz, ArH), 7.34 (d, 1H, J 8.3 Hz, H5).

Example 24

4',7-Diacetoxy-3'-methoxy-8-methylisoflavan-4-ol

4',7-Diacetoxy-3'-methoxy-8-methylisoflavan-4-ol was prepared from 4',7-diacetoxy-3'-methoxy-8-methylisoflavone (0.25g, 0.7 mmol) in methanol (50 ml) using palladium-on-charcoal (5%, 0.07g) by the method described above.

For *trans*-4',7-diacetoxy-3'-methoxy-8-methylisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H, CH_3), 2.30, 2.32 (each s, 3H, $OCOCH_3$), 3.18 (ddd, 1H, J 3.8 Hz, 8.3 Hz, 11.4 Hz, H3), 3.79 (s, 3H, OMe), 4.28 (dd, 1H, J 9.0 Hz, 11.3 Hz, H2); 4.41 (m, 1H, H2), 4.93 (d, 1H, J 7.9 Hz, H4), 6.64 (d, 1H, J 7.9 Hz, H6), 6.75-6.92 (m, ArH), 7.00 (d, 1H, J 7.9 Hz, ArH), 7.16 (d, 1H, J 8.3 Hz, ArH).

For *cis*-3',7-diacetoxy-8-methylisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H, CH_3), 2.30, 2.32 (each s, 3H, $OCOCH_3$), 3.29 (dt, 1H, J 3.4 Hz, J 11.7 Hz, H3), 4.40 (m, 1H, H2); 4.59 (t, 1H, J 10.5 Hz, H2), 4.81 (bs, 1H, H4), 6.67 (d, 1H, J 7.9 Hz, H6), 6.75-6.92 (m, ArH), 7.03 (d, 1H, J 8.3 Hz, ArH), 7.33 (d, 1H, J 8.3 Hz, ArH).

Dehydration Reactions

Example 25

4',7-Diacetoxydehydroequol (4',7-Diacetoxyisoflav-3-ene)

Method A

Distilled trifluoroacetic acid (0.1 ml) was added to a solution of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein (0.1g) in dry distilled dichloromethane (15 ml) and the mixture was refluxed under argon. Progress of the reaction was monitored by thin layer chromatography and further 0.1 ml portions of trifluoroacetic acid were added. After refluxing for 4 hours, the reaction mixture was cooled and washed successively with saturated sodium bicarbonate solution, water and brine. The resulting organic phase was dried, concentrated, chromatographed and crystallised to yield 4',7-diacetoxydehydroequol as colourless prisms (0.034g, 35%). ^{1}H NMR ($CDCl_3$ + d_6-DMSO): δ 2.29 (s, 3H, $OCOCH_3$), 2.31 (s, 3H, $OCOCH_3$), 5.15 (s, 2H, H2), 6.62 (bs, 1H, H4), 6.65 (dd, 1H, J 2.1

Hz 8.2 Hz, H6), 6.75 (bs, 1H, H8), 7.06 (d, 1H, J 8.2 Hz H5), 7.12 (d, 2H, J 8.2 Hz, ArH), 7.43 (d, 2H, J 8.2 Hz, ArH).

Method B

p-Toluenesulfonic acid (0.02 g) was added to a solution of *cis*- and *trans*-4'7-diacetoxytetrahydrodaidzein (0.1 g) in dry distilled dichloromethane (15 ml) and the mixture was refluxed under argon. Progress of the reaction was monitored by thin layer chromatography and after 4h at reflux, the reaction mixture was passed through a short column of silica gel and the eluant recrystallised from ethanol to yield 4',7-diacetoxydehydroequol as colourless prisms (0.025 g, 26%).

Method C

Phosphorous pentoxide (5g) was added with stirring to a solution of *cis*- and *trans*-4',7-diacetoxytetrahydrodaidzein (1.0g) in dry dichoromethane (80 ml). The mixture was stirred at room temperature for 2 hours and filtered through a pad of Celite. The dichoromethane solution was concentrated and chromatographed on silica gel to yield 4',7-diacetoxydehydroequol as colourless prisms (0.64g, 67%).

Example 26

7-Acetoxy-4'-methoxyisoflav-3-ene

Phosphorus pentoxide (1.0g) was added with stirring to a solution of *cis*- and *trans*-7-acetoxy-4'-methoxyisoflavan-4-ol (0.1g, 0.3 mmol) in dry dichloromethane (20 ml). The mixture was stirred at room temperature for 2 hours and filtered through a pad of Celite. The organic phase was concentrated and chromatographed on silica gel to yield 7-acetoxy-4'-methoxyisoflav-3-ene (0.04g, 42%). 1H NMR ($CDCl_3$); δ 2.28 (s, 3H, OCOCH3), 3.83 (s, 3H, OCH3), 5.14 (s, 2H, H2), 6.61 (dd, 1H, J 2.3 Hz 6.4 Hz, H6), 6.65 (d, 1H, J 2.3 Hz, H8), 6.69 (bs, 1H, H4), 6.92 (d, 2H, J 9.0 Hz ArH), 7.04 (d, 1H, J 7.9 Hz, H5), 7.37 (d, 2H, J 9.0 Hz, ArH).

Example 27

3',7-Diacetoxydehydroequol (3',7-Diacetoxyisoflav-3-ene)

3',7-Diacetoxyisoflav-3-ene was prepared from *cis*- and *trans*-3',7-diacetoxyisoflavan-4-ol (0.2g, 0.6 mmol) in dry dichloromethane (50 ml) using phosphorus pentoxide (2.0g). Yield:

(0.09g, 48%). ^{1}H NMR ($CDCl_3$): δ 2.29 and 2.32 (each s, 3H, $OCOCH_3$), 5.14 (s, 2H, H2), 6.61 (d, 1H, J 2.3 Hz, H8), 6.66 (dd, 1H, J 2.3 Hz 7.9 Hz, H6), 6.79 (bs, 1H, H4), 7.02-7.15 (m, 3H, ArH), 7.25-7.44 (m, 2H, ArH).

Example 28

7-Acetoxy-3'-methoxydehydroequol (7-Acetoxy-3'-methoxyisoflav-3-ene)

7-Acetoxy-3'-methoxyisoflav-3-ene was prepared from *cis*- and *trans*-7-acetoxy-3'-methoxyisoflavan-4-ol (0.25g, 0.8 mmol) in dry dichloromethane (20 ml) using phosphorus pentoxide (2.0g). Yield: (0.15g, 63%). ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, $OCOCH_3$), 3.85 (s, 3H, OMe), 5.15 (s, 2H, H2), 6.60-6.67 (m, 2H, ArH), 6.78 (bs, 1H, H4), 6.84-7.06 (m, 4H, ArH), 7.35 (t, 1H, J 8.6 Hz, ArH).

Example 29

4',7-Diacetoxy-3'-methoxyisoflav-3-ene

4',7-Diacetoxy-3'-methoxyisoflav-3-ene was prepared from *cis*- and *trans*-4',7-diacetoxy-3'-methoxyisoflavan-4-ol (0.20g, 0.5 mmol) in dry dichloromethane (20 ml) using phosphorus pentoxide (2.0g). Yield: (0.11g, 58%).

Example 30

7-Acetoxyisoflav-3-ene

7-acetoxyisoflav-3-ene was prepared from *cis*- and *trans*-7-acetoxyisoflavan-4-ol (0.4g, 1.4 mmol) in dry dichloromethane (60 ml) using phosphorus pentoxide (5.0g). Yield: (0.2g, 53%). ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, $OCOCH_3$), 5.18 (s, 2H, H2), 6.61-6.67 (m, 2H, ArH), 6.79 (bs, 1H, H4), 7.07 (d, 1H, J 7.9 Hz, H5), 7.23-7.45 (m, 5H, ArH).

Example 31

4',7,8-Triacetoxydehydroequol (4',7,8-Triacetoxyisoflav-3-ene)

Phosphorus pentoxide (5.0g) was added with stirring to a solution of *cis*- and *trans*-4',7,8-triacetoxyisoflavan-4-ol (0.5g, 1.3 mmol) in dry dichloromethane (50 ml). The mixture was stirred at room temperature for 2h and filtered through a pad of Celite. The resulting solution was concentrated and chromatographed on silica gel to yield *4',7,8-triacetoxyisoflav-3-ene* (0.3g, 63%). ^{1}H NMR ($CDCl_3$): δ 2.29, 2.31, 2.32, (each s, 3H,

$OCOCH_3$), 5.15 (s, 2H, H2), 6.72 (d, 1H, J 8.3 Hz, H6), 6.75 (bs, 1H, H4), 6.97 (d, 1H, J 7.9 Hz, H5), 7.12 (d, 2H, J 8.7 Hz ArH), 7.41 (d, 2H, J 8.7 Hz, ArH).

Example 32

7,8-Diacetoxy-4-methoxydehydroequol (7,8-Diacetoxy-4-methoxyisoflav-3-ene)

7,8-Diacetoxy-4-methoxyisoflav-3-ene was prepared from *cis*- and *trans*-7,8-diacetoxy-4-methoxyisoflavan-4-ol (0.4g, 1.1 mmol) in dry dichloromethane (60 ml) using phosphorus pentoxide (5.0g). Yield: (0.18g, 47%). ^{1}H NMR ($CDCl_3$): δ 2.29, 2.32 (each s, 3H, $OCOCH_3$), 3.83 (s, 3H, OCH_3), 5.14 (s, 2H, H2), 6.69 (bs, 1H, H4), 6.71 (d, 1H, J 8.3 Hz, H6), 6.90 (d, 2H, J 8.6 Hz ArH), 6.95 (d, 1H, J 7.9 Hz, H5), 7.36 (d, 2H, J 8.6 Hz, ArH).

Example 33

4',7-Diacetoxy-8-methylisoflav-3-ene

Phosphorus pentoxide (3.0g) was added with stirring to a solution of *cis*- and *trans*-4',7-diacetoxy-8-methylisoflavan-4-ol (0.55g, 1.5 mmol) in dry dichloromethane (25 ml). The mixture was stirred at room temperature for 2h and filtered through a pad of Celite. The resulting solution was concentrated and chromatographed on silica gel to yield 4',7-diacetoxy-8-methylisoflav-3-ene (0.25g, 48%). m.p. 140°C. ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3H, CH_3), 2.31, 2.32 (each s, 3H, $OCOCH_3$), 5.16 (s, 2H, H2), 6.61 (d, 1H, J 8.3 Hz, H6), 6.75 (bs, 1H, H4), 6.94 (d, 1H, J 8.3 Hz, H5), 7.13 (d, 2H, J 8.7 Hz, ArH), 7.45 (d, 2H, J 8.7 Hz, ArH). Mass spectrum: m/z 339 (M+1, 6%); 338 (M, 26); 296 (48); 254 (90); 253 (100).

Example 34

3',7-Diacetoxy-8-methylisoflav-3-ene

3',7-Diacetoxy-8-methylisoflav-3-ene was prepared from *cis*- and *trans*-3',7-diacetoxy-8-methylisoflavan-4-ol (0.25g, 0.7 mmol) in dry dichloromethane (20 ml) using phosphorus pentoxide (2.0g). Yield: (0.13g, 54%) m.p. 116°C. ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3H, CH_3), 2.31, 2.32 (each s, 3H, $OCOCH_3$), 5.16 (s, 2H, H2), 6.61 (d, 1H, J 8.3 Hz, H6), 6.79 (bs, 1H, H4), 6.92 (d, 1H, J 8.3 Hz, ArH), 7.05 (dd, 1H, J 2.0 Hz, 8.0 Hz, ArH), 7.15 (s, 1H, ArH), 7.26 (d, 1H, J 8.0 Hz, ArH), 7.37 (t, 1H, J 8.0 Hz, ArH). Mass spectrum: m/z 339 (M+1, 15%); 338 (M, 22); 296 (54); 254 (30).

Example 35

7-Acetoxy-4'-methoxy-8-methylisoflav-3-ene

7-Acetoxy-4'-methoxy-8-methylisoflav-3-ene was prepared from *cis*- and *trans*-7-acetoxy-4'-methoxy-8-methylisoflavan-4-ol (0.25g, 0.7 mmol) in dry dichloromethane (20 ml) using phosphorus pentoxide (2.0g). Yield: (0.11g, 46%) m.p. 107°C. ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3H, CH_3), 2.31 (s, 3H, $OCOCH_3$), 3.83 (s, 3H, OMe), 5.16 (s, 2H, H2), 6.59 (d, 1H, J 8.3 Hz, H6), 6.68 (bs, 1H, H4), 6.90 (d, 1H, J 8.3 Hz, H5), 6.93 (d, 2H, J 9.0 Hz, ArH), 7.37 (d, 2H, J 9.0 Hz, ArH). Mass spectrum: m/z 311 (M+1, 13%); 310 (M, 68); 267 (100); 152 (68); 135 (90).

Example 36

4',7-Diacetoxy-3'-methoxy-8-methylisoflav-3-ene

4',7-Diacetoxy-3'-methoxy-8-methylisoflav-3-ene was prepared from *cis*- and *trans*-4'.7-diacetoxy-3'-methoxy-8-methylisoflavan-4-ol (0.25g, 0.6 mmol) in dry dichloromethane (25 ml) using phosphorus pentoxide (2.0g). Yield: (0.14g, 58%) m.p. 123°C. ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H, CH_3), 2.31. 2.32 (each s, 3H, $OCOCH_3$), 3.88 (s, 3H, OMe), 5.16 (s, 2H, H2), 6.61 (d, 1H, J 8.3 Hz, H6), 6.73 (bs, 1H, H4), 6.94 (d, 1H, J 8.3 Hz, H5), 6.97 (dd, 1H, J 1.9 Hz, 8.3 Hz, ArH), 7.03 (d, 1H, J 1.9 Hz, ArH), 7.05 (d, 1H, J 7.9 Hz, ArH).

Deprotection Reactions

Example 37

Dehydroequol (Isoflav-3-ene-4',7-diol)

Imidazole (0.09 g) was added to a suspension of 4',7-diacetoxydehydroequol (0.03 g, 0.09 mmol) in absolute ethanol (2.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and the product was precipitated by addition of distilled water (10 ml). The mixture was left overnight in the fridge and filtered to yield dehydroequol. The crude product was reprecipitated from methanol by addition of benzene to yield dehydroequol as fluffy white solid (0.012 g, 55%). ^{1}H NMR ($CDCl_3$ + d_6-DMSO): δ 4.93 (s, 2H, H2), 6.26 (bs, 1H, H4), 6.29 (dd, 1H, J 2.0 Hz, 8.2 Hz, H6), 6.50 (bs, 1H, H8), 6.73 (d, 2H, J 8.2 Hz, ArH), 6.76 (d, 2H, J 8.2 Hz, H5), 7.13 (d, 2H, J 8.2 Hz, ArH).

Example 38

7-Hydroxy-4'-methoxyisoflav-3-ene

Imidazole (0.18g) was added to a suspension of 7-acetoxy-4'-methoxyisoflav-3-ene (0.06g, 0.02 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 minutes under argon. The solution was concentrated under reduced pressure and the product was precipitated by addition of distilled water (10 ml). The mixture was left overnight in the fridge and filtered to yield isoflav-3-ene. The crude product was recrystallised from methanol/benzene to yield 7-hydroxy-4'-methoxyisoflav-3-ene (0.034g, 66%). ^{1}H NMR ($CDCl_3$ + d_6-DMSO): δ 3.74 (s, 3H, OCH_3), 4.99 (s, 2H, H2), 6.21 (d, 1H, J 2.3 Hz, H8), 6.29 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.67 (bs, 1H, H4), 6.85 (d, 1H, J 8.3 Hz, H5), 6.86 (d, 2H, J 8.7 Hz, ArH), 7.33 (d, 2H, J 8.7 Hz, ArH).

Example 39

Isoflav-3-ene-3',7-diol

Isoflav-3-ene-3',7-diol was prepared from 3',7-diacetoxyisoflav-3-ene (0.09g, 0.3 mmol) and imidazole (0.3g) in ethanol (2.0 ml) as described for isoflav-3-ene-4',7-diol. Yield: (0.04g, 60%). ^{1}H NMR ($CDCl_3$ + d_6-DMSO): δ 4.94 (s, 2H, H2), 6.21 (d, 1H, J 2.0 Hz, H8), 6.29 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.62 (m, 1H, ArH), 6.64 (bs, 1H, H4), 6.75-6.82 (m, 3H, ArH), 7.07 (t, 1H, J 7.9 Hz, ArH), 8.99-9.17 (bs, 2H, OH).

Example 40

3'-MethoxyIsoflav-3-ene-7-ol

3'-MethoxyIsoflav-3-ene-7-ol was prepared from 7-acetoxy-3'-methoxyisoflav-3-ene (0.1g, 0.3 mmol) and imidazole (0.15g) in ethanol (2.0 ml) as described for isoflav-3-ene-4',7-diol. Yield: (0.06g, 70%) m.p. 75°C. ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, OMe), 5.12 (s, 2H, H2), 6.38 (d, 1H, J 2.0 Hz, H8), 6.40 (dd, 1H, J 2.0 Hz, 8.3 Hz, H6), 6.76 (bs, 1H, H4), 6.84 (dd, 1H, J 1.9 Hz, 8.3 Hz, ArH), 6.95 (m, 3H, ArH), 7.29 (t, 1H, J 8.3 Hz, ArH).

Example 41

3'-MethoxyIsoflav-3-ene-4',7-diol

3'-MethoxyIsoflav-3-ene-4',7-diol was prepared from 4',7-diacetoxy-3-methoxyisoflav-3-ene (0.11g, 0.3 mmol) and imidazole (0.3g) in ethanol (2.0 ml) as described for isoflav-3-ene-4',7-diol. Yield: (0.06g, 71%). ^{1}H NMR (d_6-acetone): δ 3.90 (s, 3H, OMe), 5.07 (s, 2H, H2), 6.31 (d, 1H, J 2.3 Hz, H8), 6.40 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.78 (bs, 1H, H4), 6.83 (d, 1H, J 8.3 Hz, ArH), 6.92 (dd, 2H, J 1.9 Hz, 8.3 Hz, ArH), 7.14 (d, 1H, J 1.9 Hz, ArH), 7.04,7.63 (each s, 1H, OH).

Example 42

Isoflav-3-ene-7-ol

Isoflav-3-ene-7-ol was prepared from 7-acetoxyisoflav-3-ene (0.2g, 0.75 mmol) and imidazole (0.24g) in ethanol (3.5 ml) as described for isoflav-3-ene-4',7-diol. Yield: (0.11g, 66%) m.p. 120°C. ^{1}H NMR (d_6-DMSO): δ 5.07 (s, 2H, H2), 6.24 (d, 1H, J 2.2 Hz, H8), 6.33 (dd, 1H, J 1.9 Hz, 7.9 Hz, H6), 6.96 (d, 1H, J 7.9 Hz, H5), 7.00 (s, 1H, H4), 7.26-7.47 (m, 5H, ArH), 9.65 (bs, 1H, OH). Mass spectrum: m/z 224 (m, 74%); 223 (100), 175 (28); 165 (23); 147 (41).

Example 43

Isoflav-3-ene-4',7,8-triol

Imidazole (0.6g) was added to a suspension of *4',7,8-triacetoxyisoflav-3-ene* (0.16g, 0.4 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and the product was precipitated by addition of distilled water (10 ml). The mixture was left overnight in the fridge and filtered to yield isoflav-3-ene. The crude product was recrystallised from methanol/benzene to yield *Isoflav-3-ene-4',7-8-triol* (0.08g, 75%). ^{1}H NMR ($CDCl_3$ + d_6-DMSO): δ 4.97 (s, 2H, H2), 6.30 (d, 1H, J 8.2 Hz, H6), 6.36 (d, 1H, J 8.3 Hz, H5), 6.55 (bs, 1H, H4), 6.72 (d, 1H, J 8.7 Hz, ArH), 7.17 (d, 2H, J 8.7 Hz, ArH).

Example 44

4'-Methoxyisoflav-3-ene-7,8-diol

4'-Methoxyisoflav-3-ene-7,8-diol was prepared from 7,8-diacetoxy-4-methoxyisoflav-3-ene (0.15g, 0.4 mmol) and imidazole (0.4g) in ethanol (1.6 ml) as described for isoflav-3-ene-4',7-8-triol. Yield: (0.73g, 61%). ^{1}H NMR ($CDCl_3$ + d_6-DMSO): δ 3.83 (s, 3H, OCH_3),

5.15 (s, 2H, H2), 6.51 (d, 1H, J 8.3 Hz, H6), 6.58 (d, 1H, J 8.3 Hz, H5), 6.68 (bs, 1H, H4), 6.92 (d, 1H, J 8.7 Hz, ArH), 7.35 (d, 2H, J 8.7 Hz, ArH). Mass spectrum: m/z 270 (M, 5%); 256 (100); 255 (70); 239 (20); 181 (25).

Example 45

8-Methylisoflav-3-ene-4',7-diol

Imidazole (0.6g) was added to a suspension of 4',7-diacetoxy-8-methylisoflav-3-ene (0.25g, 0.7 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and the product was precipitated by addition of distilled water (10 ml). The mixture was left overnight in the fridge and filtered to yield isoflav-3-ene. The crude product was recrystallised from methanol/benzene to yield 8-methylisoflav-3-ene-4',7-diol (0.13g, 68%). m.p. 190-93°C ^{1}H NMR ($CDCl_3$ + d_6-DMSO): δ 1.94 (s, 3H, CH_3), 4.98 (s, 2H, H2), 6.32 (d, 1H, J 7.9 Hz, H6), 6.58 (bs, 1H, H4), 6.67 (bd, 1H, H5), 6.72 (d, 2H, J 8.7 Hz, ArH), 7.21 (bd, 2H, ArH). Mass spectrum: m/z 255 (M+1, 16%); 254 (M, 79); 253 (100); 161 (32).

Example 46

8-Methylisoflav-3-ene-3',7-diol

8-Methylisoflav-3-ene-3',7-diol was prepared from 3',7-diacetoxy-8-methylisoflav-3-ene (0.12g, 0.4 mmol) and imidazole (0.3g) in ethanol (2.5 ml) as described for 8-methylisoflav-3-ene-4',7-diol. Yield: (0.07g, 77%) m.p. 130°C. ^{1}H NMR ($CDCl_3$ + d_6-DMSO): δ 1.95 (s, 3H, CH_3), 4.98 (s, 2H, H2), 6.34 (d, 1H, J 8.0 Hz, H6), 6.61-6.94 (m, 5H, ArH), 7.08 (bt, 1H, ArH). Mass spectrum: m/z 254 (M, 100%); 253 (96); 161 (45).

Example 47

4'-Methoxy-8-methylisoflav-3-ene-7-ol

4'-Methoxy-8-methylisoflav-3-ene-7-ol was prepared from 7-acetoxy-4'-methoxy-8-methylisoflav-3-ene (0.11g, 0.3 mmol) and imidazole (0.14g) in ethanol (1.5 ml) as described for 8-methylisoflav-3-ene-4',7-diol. Yield: (0.05g, 53%) m.p. 103°C. ^{1}H NMR (d_6-acetone): δ 1.99 (s, 3H, CH_3), 3.81 (s, 3H, OMe), 5.11 (s, 2H, H2), 6.43 (d, 1H, J 8.3 Hz, H6), 6.77 (bs, 1H, H4), 6.80 (d, 1H, J 8.3 Hz, H5), 6.95 (d, 2H, J 9.0 Hz, ArH), 7.44 (d, 2H, J 9.0 Hz, ArH). Mass spectrum: 282 (M, 9%); 267 (100); 268 (95); 134 (52).

Example 48

3'-Methoxy-8-methylisoflav-3-ene-4',7-diol

3'-Methoxy-8-methylisoflav-3-ene-4',7-diol was prepared from 4',7-diacetoxy-3'-methoxy-8-methylisoflav-3-ene (0.21g, 0.6 mmol) and imidazole (0.52g) in ethanol (4 ml) as described for 8-methylisoflav-3-ene-4',7-diol. Yield: (0.1g, 63%). ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H, CH_3), 3.94 (s, 3H, OMe), 5.11 (s, 2H, H2), 6.42 (d, 1H, J 8.3 Hz, H6), 6.64 (bs, 1H, ArH), 6.80 (d, 1H, J 7.9 Hz, ArH), 6.94 (m, 2H, ArH), 7.12 (m, 1H, ArH), 7.26, 7.70 (each bs, 1H, OH).

Deprotection Reactions

Example 49

***cis*- and *trans*-Tetrahydrodaidzein**

Imidazole (0.2 g) was added to a suspension of 4',7-diacetoxytetrahyrodaidzein (0.10 g, 0.3 mmol) in absolute ethanol (4.0 ml) and the mixture refluxed for 45 min under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added. The mixture was left overnight in the fridge and the crystalline product was filtered to yield *cis*- and *trans*-tetrahydrodaidzein (0.06 g, 80%).

Example 50

***trans*-Tetrahydrodaidzein (*trans*-4',7-Dihydroxyisoflavan-4-ol)**

Trans-4',7-dihydroxyisoflavan-4-ol was prepared from *trans*-4',7-dihydroxyisoflavan-4-ol and imidazole in ethanol as described for *cis*- and *trans*-tetrahydrodaidzein. ^{1}H NMR (d_6-acetone): δ 2.99 (ddd, 1H, J 3.4 Hz, 6.8 Hz, 10.6 Hz, H3), 4.13 (dd, 1H, J 7.0 Hz, 10.9 Hz, H2); 4.24 (dd, 1H, J 3.8 Hz, 11.3 Hz, H2), 4.70 (d, 1H, J 6.4 Hz, H4), 6.20 (d, 1H, J 2.6 Hz, H8), 6.38 (dd, 1H, J 2.3 Hz, 8.3 Hz, H6), 6.71 (d, 2H, J 8.7 Hz, ArH), 7.04 (d, 2H, J 8.7 Hz, ArH), 7.18 (d, 1H, J 8.3 Hz, H5).

Example 51

***cis*- and *trans*-7-Hydroxy-4'-methoxyisoflavan-4-ol**

Imidazole (0.4 g) was added to a suspension of 7-acetoxy-4'-methoxyisoflavan-4-ol (0.20 g, 0.6 mmol) in absolute ethanol (8.0 ml) and the mixture refluxed for 45 minutes under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added. The mixture was left overnight in the fridge and the crystalline product was filtered to yield *cis*- and *trans*-7-hydroxy-4'-methoxyisoflavan-4-ol (0.16g, 79%).

Example 52

***cis*- and *trans*-7-Hydroxyisoflavan-4-ol**

7-hydroxyisoflavan-4-ol was prepared from 7-acetoxyisoflavan-4-ol (0.14g, 0.5 mmol) and Imidazole (0.17g) in ethanol (3.0 ml) as described for *cis*- and *trans*-tetrahydrodaidzein.

For *trans*-7-hydroxyisoflavan-4-ol; ^{1}H NMR (d_6-acetone): δ 3.08 (m, 1H, H3), 4.00 (t, 1H, J 10.2 Hz, H2); 4.30 (m, 1H, H2), 4.81 (d, 1H, J 7.2 Hz, H4), 6.25-6.43 (m, ArH), 6.89 (d, J 8.3 Hz, ArH), 7.07 (d, J 8.3 Hz, ArH), 7.22-7.64 (m, ArH).

For *cis*-7-acetoxyisoflavan-4-ol; ^{1}H NMR (d_6-acetone): δ 3.20 (m, 1H, H3), 4.36 (m, 1H, H2); 4.57 (dd, 1H, J 10.2 Hz, 12.0 Hz, H2), 4.68 (bs, 1H, H4), 6.25-6.43 (m, ArH), 6.89 (d, J 8.3 Hz, ArH), 7.07 (d, J 8.3 Hz, ArH), 7.22-7.64 (m, ArH).

Example 53

***cis*- and *trans*-4',7-Dihydroxy-8-methylisoflavan-4-ol**

4',7-Dihydroxy-8-methylisoflavan-4-ol was prepared from 4',7-diacetoxy-8-methylisoflavan-4-ol (0.4g, 1.1 mmol) and imidazole (1.0g) in ethanol (7.0 ml) as described for *cis*- and *trans*-tetrahydrodaidzein.

For *trans*-4',7-dihydroxy-8-methylisoflavan-4-ol; ^{1}H NMR (d_6-acetone): δ 1.98 (s, 3H, CH_3), 2.98 (ddd, 1H, J 3.8 Hz, 10.9 Hz, 12.0 Hz, H3), 4.18 (m, 1H, H2); 4.27 (m, 1H, H2), 4.75 (d, 1H, J 6.4 Hz, H4), 6.42 (m, ArH), 6.75 (m, ArH), 7.05-7.19 (m, ArH), 7.66 (bs, OH).

For *cis*-4',7-dihydroxy-8-methylisoflavan-4-ol; ^{1}H NMR (d_6-acetone): δ 1.99 (s, 3H, CH_3), 3.01 (dt, 1H, J 3.4 Hz, 12.0 Hz, H3), 4.31 (m, 1H, H2); 4.52 (dd, 1H, J 10.2 Hz, 12.0 Hz, H2), 4.60 (bs, 1H, H4), 6.42 (m, ArH), 6.75 (m, ArH), 7.05-7.19 (m, ArH), 7.66 (bs, OH).

Example 54

***trans*-7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol**

trans-7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol was prepared from *trans*-7-acetoxy-4'-methoxy-8-methylisoflavan-4-ol (0.23g, 0.7 mmol) and imidazole (0.28g) in ethanol (2.1 ml) as described for *cis*- and *trans*-tetrahydrodaidzein. m.p. 162°C. Mass spectrum: 285 M, 5%); 268 (10); 151 (20); 135 (20); 134 (100); 119 (20). ^{1}H NMR (d_6-acetone): δ 1.97 (s, 3H, CH_3), 3.00 (ddd, 1H, J 3.4 Hz, 7.2 Hz, 10.2 Hz, H3), 3.72 (s, 3H, OMe), 4.20 (dd, 1H, J 7.5 Hz, 10.9 Hz, H2); 4.27 (m, 1H, H2), 4.73 (d, 1H, J 6.8 Hz, H4), 6.45 (d, 1H, J 8.3 Hz, H6), 6.85 (d, 2H, J 8.6 Hz, ArH), 7.10 (d, 1H, J 8.7 Hz, H5), 7.18 (d, 2H, J 8.6 Hz, ArH).

Hydrogenation Reactions:– Isoflavone → cis-Isoflavan-4-ol

Example 55

***cis*-4',7-Diacetoxyisoflavan-4-ol**

Platinum(IV)oxide (Adam's catalyst) (0.05g) was added to a solution of of 4',7-diacetoxyisoflavanone (0.25g, 0.7 mmol) in ethyl acetate (40 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 55h. The catalyst was removed by filtration through Celite and the filtrate was evaporated *in vacuo* to yield predominantly the *cis*-4',7-diacetoxyisoflavan-4-ol.

For *cis*-4',7-diacetoxyisoflavan-4-ol; ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, $OCOCH_3$), 2.29 (s, 3H, $OCOCH_3$), 3.30 (dt, 1H, J 3.4 Hz, J 11.8 Hz, H3), 4.31 (ddd, 1H, J 1.4 Hz, 3.6 Hz, 10.5 Hz, H2); 4.56 (dd, 1H, J 10.5 Hz, 11.8 Hz, H2), 4.75 (dd, 1H, J 1.3 Hz, 3.2 Hz, H4), 6.66 (dd, 1H, J 2.3 Hz, 8.7 Hz, H6),6.69 (d, 1H, J 2.3 Hz, H8), 7.08 (d, 2H, J 8.6 Hz, ArH), 7.26 (d, 1H, 8.4 Hz, H5), 7.29 (d, 2H, J 8.6 Hz, ArH). ^{13}C NMR ($CDCl_3$): δ 20.98 ($OCOCH_3$), 43.52 (C3), 64.10 (C2), 66.46 (C4), 110.08 (C6), 114.09 (C8), 121.82, 129.40 (ArCH), 131.10 (C5).

Hydrogenation Reactions:– Isoflavone → Isoflavan-4-one

Example 56

4',7-Diacetoxydihydrodaidzein (4',7-Diacetoxyisoflavan-4-one)

Palladium-on-charcoal (5%, 0.02g) was added to a solution of 4',7-diacetoxydaidzein (0.50g, 1.5 mmol) in ethyl acetate (80 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 72h. The catalyst was removed by filtration through Celite and the resulting filtrate was evaporated *in vacuo*. The residue was recrystallised from ethanol to yield 4',7-diacetoxydihydrodaidzein (0.40g, 80%) as colourless plates. ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, $OCOCH_3$), 2.23 (s, 3H, $OCOCH_3$), 3.98 (dd, 1H, J 6.2 Hz, 8.2 Hz, H3), 4.69 (m, 2H, H2), 6.78-6.82 (m, 2H, ArH), 7.08 (d, 2H, J 9.2 Hz, ArH), 7.30 (d, 2H, J 8.2 Hz, ArH), 7.98 (d, 1H, J 9.2 Hz H5).

Hydrogenation Reactions:– Isoflavan-3-ene → Isoflavan

Example 57

O,O-Diacetylequol

Palladium-on-charcoal (5%, 0.02g) was added to a solution of 4',7-diacetoxyisoflav-3-ene (0.20g, 0.06 ml) in ethyl acetate (60 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 24h. The catalyst was removed by filtration through Celite and the resulting filtrate was evaporated *in vacuo*. The residue was recrystallised from dichloromethane/light petroleum to yield O,O-diacetylequol (0.15g, 75%). ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, $OCOCH_3$), 2.31 (s, 3H, $OCOCH_3$), 3.00 (d, 2H, J 8.3 Hz, H4), 3.25 (m, 1H, H3), 4.00 (t, 1H, H2), 4.34 (dd, 1H, J 3.4 Hz, 10.9 Hz, H2), 6.61 (d, J 7.5 Hz, 1H, ArH), 6.60 (s, 1H, ArH), 7.06 (bd, 3H, J 8.3 Hz, ArH), 7.24 (d, 3H, J 8.3 Hz, ArH).

Deprotection Reactions

Example 58

Dihydrodaidzein (4',7-Dihydroxyisoflavan-4-one)

Imidazole (0.63g) was added to a suspension of 4',7-diacetoxydihydrodaidzein (0.26g, 0.08 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon.

The solution was concentrated under reduced pressure and distilled water (10 ml) was added to the residue. The mixture was left overnight in the fridge and the resulting precipitate was filtered. The crude product was recrystallised from ethyl aceate/dichloromethane to yield 4',7-diacetoxydihydrodaidzein (0.14g, 71%) as a white powder. ^{1}H NMR (d_6-acetone): δ 3.83 (t, 1H, J 7.2 Hz, H3), 4.60 (d, 2H, J 6.2 Hz, H2), 6.39 (d, 1H, J 2.0 Hz, H8), 6.55 (dd, 1H, J 8.2, J 2.0 Hz, ArH), 6.80 (d, 2H, J 8.2 Hz, ArH), 7.10 (d, 1H, J 8.2 Hz, ArH), 7.74 (d, 1H, J 8.2 Hz, H5).

Example 59

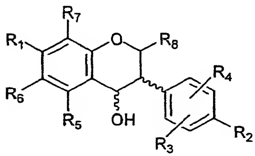
Equol (4',7-Dihydroxyisoflavan)

Imidazole 0.5g) was added to a suspension of O,O-diacetylequol (0.15g, 0.08 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added to the residue. The mixture was left overnight in the fridge and the resulting product was filtered to yield equol (0.09g, 80%) as a white powder. ^{1}H NMR (d_6-DMSO): δ 2.70 (d, 2H, J 9.2 Hz, H4), 2.92 (m, 1H, H3), 3.73 (t, 1H, J 10.3 Hz, H2), 4.06 (dd, 1H, J 3.0 Hz, 11.2 Hz, H2), 6.16 (bs, 1H, ArH), 6.21 (bd, J 8.2 Hz, 1H, ArH), 6.63 (d, 2H, J 8.2 Hz, ArH), 6.69 (d, 1H, J 8.2 Hz, ArH), 6.87 (d, 2H, J 8.2 Hz, ArH)

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The inventions also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

The claims defining the invention are as follows:

1. A method for the preparation of a compound of formula II



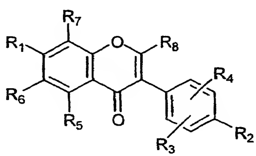
(II)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro, or halo, and

R_9 is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl,

comprising the step of hydrogenating a compound of formula I



(I)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above

to prepare a compound of formula II.

2. A method of claim 1, wherein the hydrogenation step is performed with hydrogen in the presence of a reduction catalyst and a solvent.

3. A method of claim 2, wherein the reduction catalyst comprises palladium, palladium hydroxide, platinum or platinum oxide.

4. A method of claim 3, wherein the reduction catalyst is palladium on activated carbon, palladium on barium sulfate or platinum(IV)oxide.

5. A method of claim 4, wherein the reduction catalyst is palladium on activated carbon (1% Pd to 10% Pd).

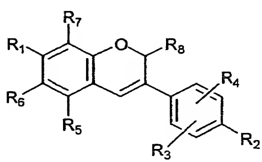
6. A method of claim 5, wherein the reduction catalyst is about 5% palladium on activated carbon.

7. A method of claim 2, wherein the solvent is a C_1-C_8 alcohol, an alkyl acetate or a C_1-C_3 carboxylic acid.

8. A method of claim 7, wherein the solvent is a methanol, ethanol or C_1-C_6 alkyl acetate.

9. A method of claim 8, wherein the solvent is absolute methanol or absolute ethanol.

10. A method of claim 1 which further comprises the step of dehydrating and optionally deprotecting or transforming a compound of formula II to prepare a compound of formula III



(III)

R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro, or halo, and

R_9 is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl.

11. A method of any one of claims 1 to 10, wherein the compounds of formula I, II or III have the following substituents

R_1 is hydroxy, OR_9 or $OC(O)R_9$,

R_2, R_3, R_4, R_5, R_6 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or arylalkyl,

R_8 is hydrogen, and

R_9 is methyl, ethyl, propyl, isopropyl or trifluoromethyl.

12. A method of claim 11, wherein the compounds of formula I, II or III have the following substituents

R_1 is hydroxy, OR_9 or $OC(O)R_9$,

R_2, R_3, R_4, R_5 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or arylalkyl,

R_6 and R_8 are hydrogen, and

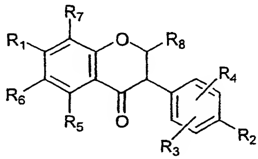
R_9 is methyl.

13. A method of any one of claims 1 to 12, wherein the compound of formula I is 4',7-diacetoxyisoflavone (daidzein diacetate) or 7-acetoxy-4'-methoxyisoflavone.

14. A method of any one of claims 1 to 13, wherein the compound of formula II is 4',7-diacetoxyisoflavan-4-ol (tetrahydrodaidzein diacetate) or 7-acetoxy-4'-methoxyisoflavan-4-ol.

15. A method of any one of claims 10 to 14, wherein and the compound of formula III is 4',7-diacetoxyisoflav-3-ene (dehydroequol diacetate), 4',7-dihydroxyisoflav-3-ene (dehydroequol), 7-acetoxy-4'-methoxyisoflav-3-ene or 7-hydroxy-4'-methoxyisoflav-3-ene.

16. A method for the preparation of a compound of formula IV



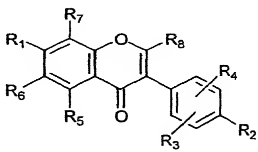
(IV)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro, or halo, and

R_9 is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl,

comprising the step of hydrogenating a compound of formula I



(I)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above to prepare a compound of formula IV.

17. A method of claim 16, wherein the hydrogenation step is performed with hydrogen in the presence of a reduction catalyst and a solvent.

18. A method of claim 17, wherein the reduction catalyst comprises palladium, palladium hydroxide, platinum or platinum(IV)oxide.

19. A method of claim 18, wherein the reduction catalyst is palladium on activated carbon (1% Pd to 10% Pd).

20. A method of claim 19, wherein the reduction catalyst is about 5% palladium on activated carbon.

21. A method of claim 17, wherein the solvent is a C_1-C_8 alcohol, a C_1-C_6 alkyl acetate or a C_1-C_3 carboxylic acid.

22. A method of claim 21, wherein the solvent is absolute methanol, ethanol or ethyl acetate.

23. A method of any one of claims 16 to 22, wherein the compound of formula I is 4',7-diacetoxyisoflavone (daidzein diacetate) or 7-acetoxy-4'-methoxyisoflavone.

24. A method of any one of claims 16 to 22, wherein the compound of formula IV has the following substituents

R_1 is hydroxy, OR_9 or $OC(O)R_9$,

R_2, R_3, R_4, R_5, R_6 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or arylalkyl,

R_8 is hydrogen, and

R_9 is methyl, ethyl, propyl, isopropyl or trifluoromethyl.

25. A method of claim 24, wherein the compound of formula IV has the following substituents

R_1 is hydroxy, OR_9 or $OC(O)R_9$,

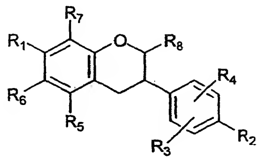
R_2, R_3, R_4, R_5 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or arylalkyl,

R_6 and R_8 are hydrogen, and

R_9 is methyl.

26. A method of claim 25, wherein the compound of formula IV is 4',7-diacetoxyisoflavan-4-one (diacetoxydihydrodaidzein) or 4',7-dihydroxyisoflavan-4-one (dihydrodaidzein).

27. A method for the preparation of a compound of formula V



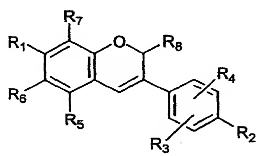
(V)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro, or halo, and

R_9 is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl,

comprising the step of hydrogenating a compound of formula III



(III)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above

to prepare a compound of formula V.

28. A method of claim 27, wherein the hydrogenation step is performed with hydrogen in the presence of a reduction catalyst and a solvent.

29. A method of claim 28, wherein the reduction catalyst comprises palladium, palladium hydroxide, platinum or platinum(IV)oxide.

30. A method of claim 29, wherein the reduction catalyst is palladium on activated carbon (1% Pd to 10% Pd).

31. A method of claim 30, wherein the reduction catalyst is about 5% palladium on activated carbon.

32. A method of claim 28, wherein the solvent is a C_1-C_8 alcohol, a C_1-C_6 alkyl acetate or a C_1-C_3 carboxylic acid.

33. A method of claim 32, wherein the solvent is a methanol, ethanol or ethyl acetate.

34. A method of claim 33, wherein the solvent is ethyl acetate.

35. A method of any one of claims 27 to 34, wherein and the compound of formula III is 4',7-diacetoxyisoflav-3-ene (dehydroequol diacetate), 4',7-dihydroxyisoflav-3-ene (dehydroequol), 7-acetoxy-4'-methoxyisoflav-3-ene or 7-hydroxy-4'-methoxyisoflav-3-ene.

36. A method of any one of claims 27 to 34, wherein the compound of formula V has the following substituents

R_1 is hydroxy, OR_9 or $OC(O)R_9$,

R_2, R_3, R_4, R_5, R_6 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or arylalkyl,

R_8 is hydrogen, and

R_9 is methyl, ethyl, propyl, isopropyl or trifluoromethyl.

37. A method of claim 36, wherein the compound of formula V has the following substituents

R_1 is hydroxy, OR_9 or $OC(O)R_9$,

R_2, R_3, R_4, R_5 and R_7 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or arylalkyl,

R_6 and R_8 are hydrogen, and

R_9 is methyl.

38. A method of claim 37, wherein the compound of formula V is 4',7-diacetoxyisoflavan (equol diacetate) or 4',7-dihydroxyisoflavan (equol).

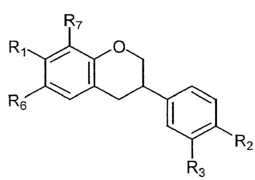
39. Methods substantially as hereinbefore described especially with reference to the Examples.

40. Compounds of formula II or formula III or formula IV or formula V when prepared by a method of any preceding claim.

41. A compound of the formulae II, III, IV or V,
wherein
R_1 is hydroxy, OR_9, $OC(O)R_9$, thio, alkylthio, or halo,
R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, aryl, thio, alkylthio or halo, and
R_9 is alkyl, fluoroalkyl or arylalkyl

with the proviso that
at least one of R_5, R_6 and R_7 is not hydrogen, or
when R_5, R_6 and R_7 are all hydrogen, then R_3 is hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, aryl, thio, alkylthio or halo,

provided that compounds of the formula



wherein

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R_1 is hydroxy or acetoxy,

R_2 is hydrogen, hydroxy, acetoxy, methoxy, methyl, isopropyl or halo,

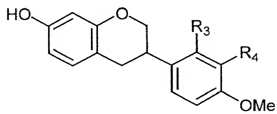
R_3 is hydrogen, methoxy, methyl, halo or trifluoromethyl,

R_6 is hydrogen, hydroxy or acetoxy, and

R_7 is hydrogen, hydroxy, methyl or methoxy

are specifically excluded,

provided that compounds of the formula



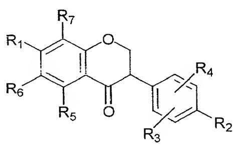
wherein

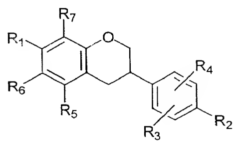
R_3 is hydroxy or methoxy, and

R_4 is hydrogen or methoxy

are specifically excluded,

provided that compounds of the formulae





wherein

R_1 is hydroxy, methoxy, ethoxy, methylthio or halogen, and

R_2, R_3 R_4, R_5, R_6, and R_7 are independently hydrogen, hydroxy, methoxy, ethoxy, methylthio or halogen,

are specifically excluded, and

provided that the compounds
4',7-Dihydroxy-3',5'-dimethoxyisoflavan-4-one
4',5-Dimethoxy-7-hydroxy-8-methylisoflavan-4-one
2',7-Dihydroxy-4',8-dimethoxyisoflavan-3-ene
are specifically excluded.

42. A compound of claim 41,
wherein
R_1 is hydroxy, OR_9 or $OC(O)R_9$,
R_2 and R_3 are independently hydrogen, hydroxy, OR_9 or $OC(O)R_9$,
R_4, R_5, R_6, and R_8 are hydrogen,
R_7 is hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or halo, and
R_9 is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl.

43. A compound of claim 41,
wherein
R_1 is hydroxy, OR_9 or $OC(O)R_9$,
R_2 and R_3 are independently hydrogen, hydroxy, OR_9 or $OC(O)R_9$,
R_5 is OR_9, $OC(O)R_9$, alkyl, aryl or halo,
R_4, R_6, R_7, and R_8 are hydrogen, and
R_9 is methyl, ethyl, propyl, isopropyl, trifluoromethyl or benzyl.

44. A compound of formula I selected from the group consisting of:
4',7,8-Triacetoxyisoflavone
7,8-Diacetoxy-4'-methoxyisoflavone
4',7-Diacetoxy-8-methylisoflavone
3',7-Diacetoxy-8-methylisoflavone
7-Acetoxy-4'-methoxy-8-methylisoflavone
4',7-Diacetoxy-3'-methoxy-8-methylisoflavone
4',5,7-Triacetoxyisoflavone

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45. A compound of formula II selected from the group consisting of:

4',7,8-Triacetoxyisoflavan-4-ol
7,8-Diacetoxy-4-methoxyisoflavan-4-ol
4',7-Diacetoxy-8-methylisoflavan-4-ol
3',7-Diacetoxy-8-methylisoflavan-4-ol
7-Acetoxy-4'-methoxy-8-methylisoflavan-4-ol
4',7-Diacetoxy-3'-methoxy-8-methylisoflavan-4-ol
4',5,7-Triacetoxyisoflavan-4-ol

4',7,8-Trihydroxyisoflavan-4-ol
7,8-Dihydroxy-4-methoxyisoflavan-4-ol
4',7-Dihydroxy-8-methylisoflavan-4-ol
3',7-Dihydroxy-8-methylisoflavan-4-ol
7-Hydroxy-4'-methoxy-8-methylisoflavan-4-ol
4',7-Dihydroxy-3'-methoxy-8-methylisoflavan-4-ol
4',5,7-Trihydroxyisoflavan-4-ol

46. A compound of formula III selected from the group consisting of:

4',7,8-Triacetoxydehydroequol (4',7,8-Triacetoxyisoflav-3-ene)
7,8-Diacetoxy-4-methoxydehydroequol (7,8-Diacetoxy-4-methoxyisoflav-3-ene)
4',7-Diacetoxy-8-methylisoflav-3-ene
3',7-Diacetoxy-8-methylisoflav-3-ene
7-Acetoxy-4'-methoxy-8-methylisoflav-3-ene
4',7-Diacetoxy-3'-methoxy-8-methylisoflav-3-ene
4',5,7-Triacetoxyisoflav-3-ene

Isoflav-3-ene-4',7,8-triol
4'-Methoxyisoflav-3-ene-7,8-diol
8-Methylisoflav-3-ene-4',7-diol
8-Methylisoflav-3-ene-3',7-diol

4'-Methoxy-8-methylisoflav-3-ene-7-ol

3'-Methoxy-8-methylisoflav-3-ene-4',7-diol

Isoflav-3-ene-4',5,7-triol

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PRODUCTION OF ISOFLAVONE DERIVATIVES

the specification of which:

is attached hereto; or

was filed as United States Application Serial No. ____________
on July 20, 2001 , and was amended on ________________
(if applicable); or

was filed as PCT International Application Number PCT/AU00/00103
on February 15, 2000 and was amended on May 4, 2001
(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate or § 365(a) of any PCT international application(s), designating at least one country other than the United States, listed below and have also identified below any foreign application(s) for patent or inventor's certificate, or any PCT international application(s) having a filing date before that of the application(s) of which priority is claimed:

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
Australia	PP 8685	February 15, 1999	☒ YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Number	Date of Filing

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT international application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

Application Number	Date of Filing	Status (Patented, Pending, Abandoned)

I hereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Reg. No. 22,540**, Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewis, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Dirk D. Thomas, Reg. No. 32,600; Thomas W. Banks, Reg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M. Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; and Linda A. Wadler, Reg. No. 33,218; Jeffrey A. Berkowitz, Reg. No. 36,743; Michael R. Kelly, Reg. No. 33,921; James B. Monroe, Reg. No. 33,971; Doris Johnson Hines, Reg. No. 34,629; Allen R. Jensen, Reg. No. 28,224; Lori Ann Johnson, Reg. No. 34,498; and David A. Manspeizer, Reg. No. 37,540 and ______________________________. Please address all correspondence to **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.,** 1300 I Street, N.W., Washington, D.C. 20005, Telephone No. (202) 408-4000.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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